Gram : UNIVERSITY
Fax : 0281-2578512

Phone : (R) 2577392
(O) 2578512

SAURASHTRA UNIVERSITY

University Road,
Rajkot - 360 005.

Dr. H. H. PAREKH
M.Sc., Ph.D., F. I. C.
Ex. Professor and Head,
Department of Chemistry

Residence :
'RASDHARA'
32-B, University
Karmachari Co. Society,
University Road,
Rajkot - 360 005.
GUJARAT (INDIA)

No.

Dt. 11-12-2006.

Statement under o. Ph. D. 7 of Saurashtra University

The work included in the thesis is my own work under the supervision of ***Dr. H. H. Parekh*** and leads to some contribution in chemistry subsidised by a number of references.

Dt. :11- 12 - 2006
Place : Rajkot.

(Nandalal V. Shekhada)

This is to certify that the present work submitted for the Ph. D. Degree of Saurashtra University by ***Nandalal V. Shekhada*** is his own work and leads to the advancement in the knowledge of chemistry. The thesis has been prepared under my supervision.

Date : 11 - 12 - 2006
Place : Rajkot.

Dr. H. H. PAREKH
Former Professor and Head,
Department of Chemistry,
Saurashtra University
Rajkot - 360 005.

Acknowledgements

My humble salute to the most revered devine Spirit, Deity, Stream of Inspirations, Omnipotent, Almighty God, Shree Krishna without whom it would have been difficult for me to reach the plateau in every sphere of my educational life.

It gives me an immense pleasure to reveal my profound respect and gratitude to the one and only esteemed, extraordinary, ingenious most efficient, the glorious fountain and continuous source of inspiration Dr. (Mrs.) H. H. Parekh, former Professor and Head, Department of Chemistry, Saurashtra University, Rajkot who held the torch of excellent guidance and lit up the darkness with the encouragement and constructive criticism towards the goal of my academic journey.

Endless Process of enlightenment has been initiated by important milestone, most learned, affectionate yet noncompromising by nature Dr. A. R. Parikh, former Professor and Head, Department of Chemistry, Saurashtra University, Rajkot. I am truly obliged by the tremendous efforts put in by him at different stages to make my educational expedition successful.

It's indeed a great pleasure to express my extreme indebtness to Dr. R. C. Khunt, Asst. Professor, Department of Chemistry, Saurashtra University, Rajkot for her invaluable guidance and encouragement through out the course of my study.

Nobody is able to give justice in giving entirely and adequately thanks to parents for giving gift of life and nurturing it. My words fail to express my feeling and acknowledging the tremendous debt to my esteemed father Vithalbhai and my loving and caring mother Kusumben and most venerated late grand father Karmshibhai and grand mother Naduben. I can never ever forget my beloved sister, Gita and my jijaji, Bhavesh brother Girdhar and sister in law Reena.

I offer my heartly gratitude to my friends & colleageus Vishal, Thanki, Shukla, Arti, Rokad, Rajendra, Mira, Mathukiya, Jimmy, Niral and also my seniors Ronak, Ashish & Viral who ever stood beside me with their helping hands and moral support. I gratefully thank all for their help and co-ordination extended by them.

I am truely thankful to non teaching staff of my department particularly Mr. Harshad Joshi, Mrs. Namrata and Govindbhai for their kind support.

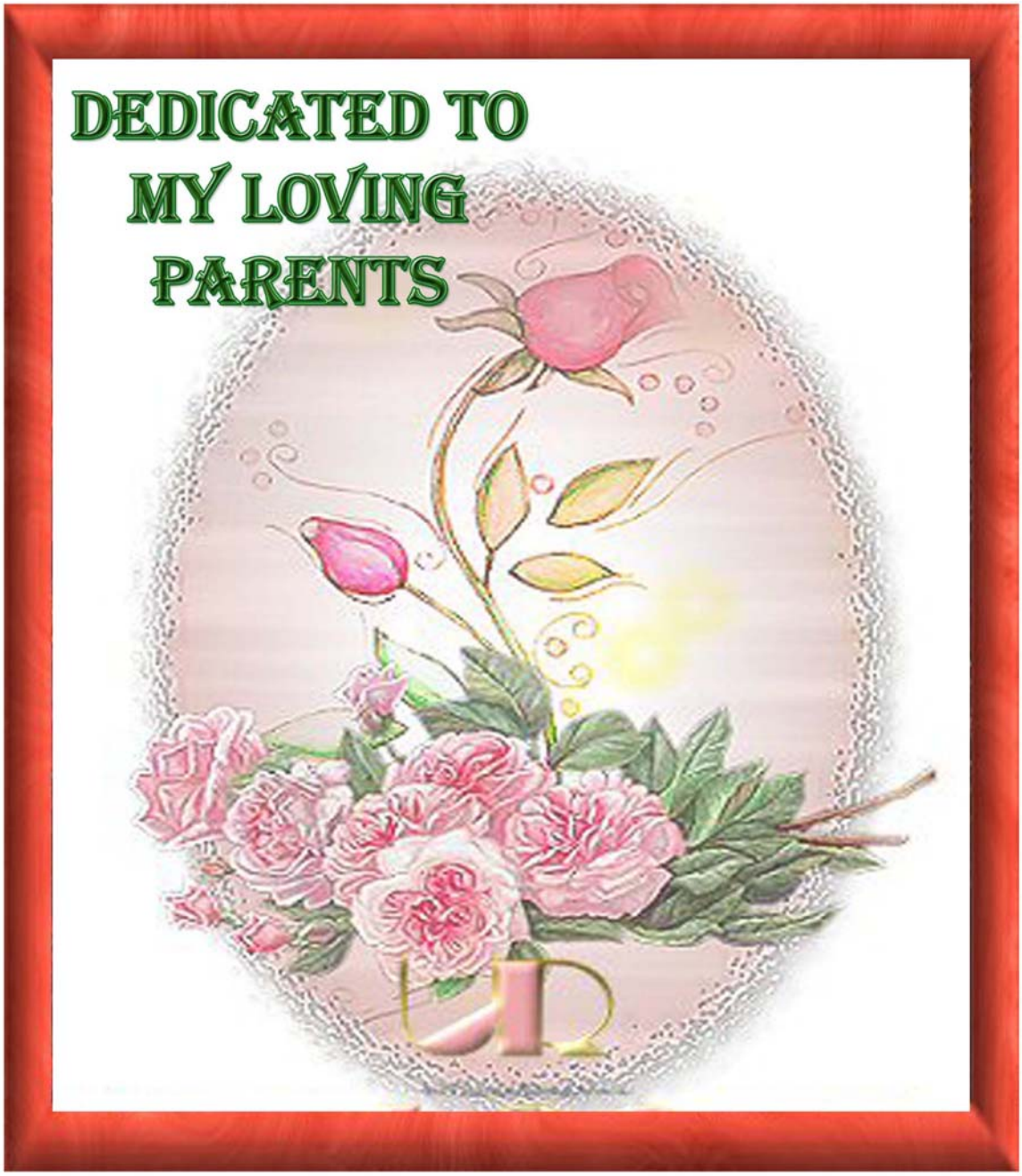
Numerous people have encouraged me and extended support to this work, which has enabled me to complete this thesis. So, I thank everyone who has played vital role either directly or indirectly for preparation of this work.

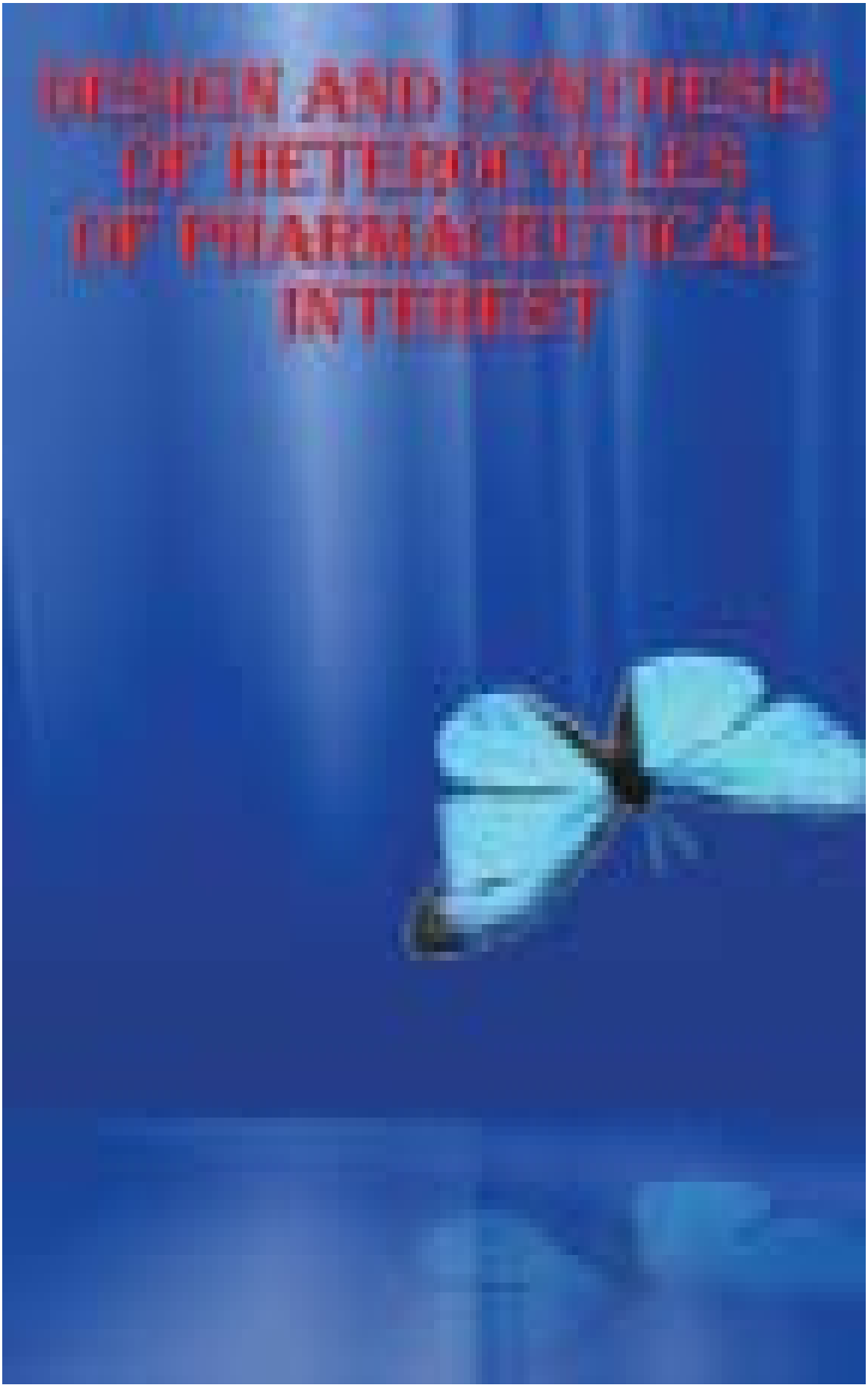
I am thankful to authorities of CDRI - Lucknow, CIL Chandigarh, for spectral studies and Mr. Pankaj Kachhadia for the mass spectral analysis and Tuberculosis Antimicrobial Acquisition Coordination facility, Alabama, U.S.A., for kind co-operation extended by them for antituberculosis activity.

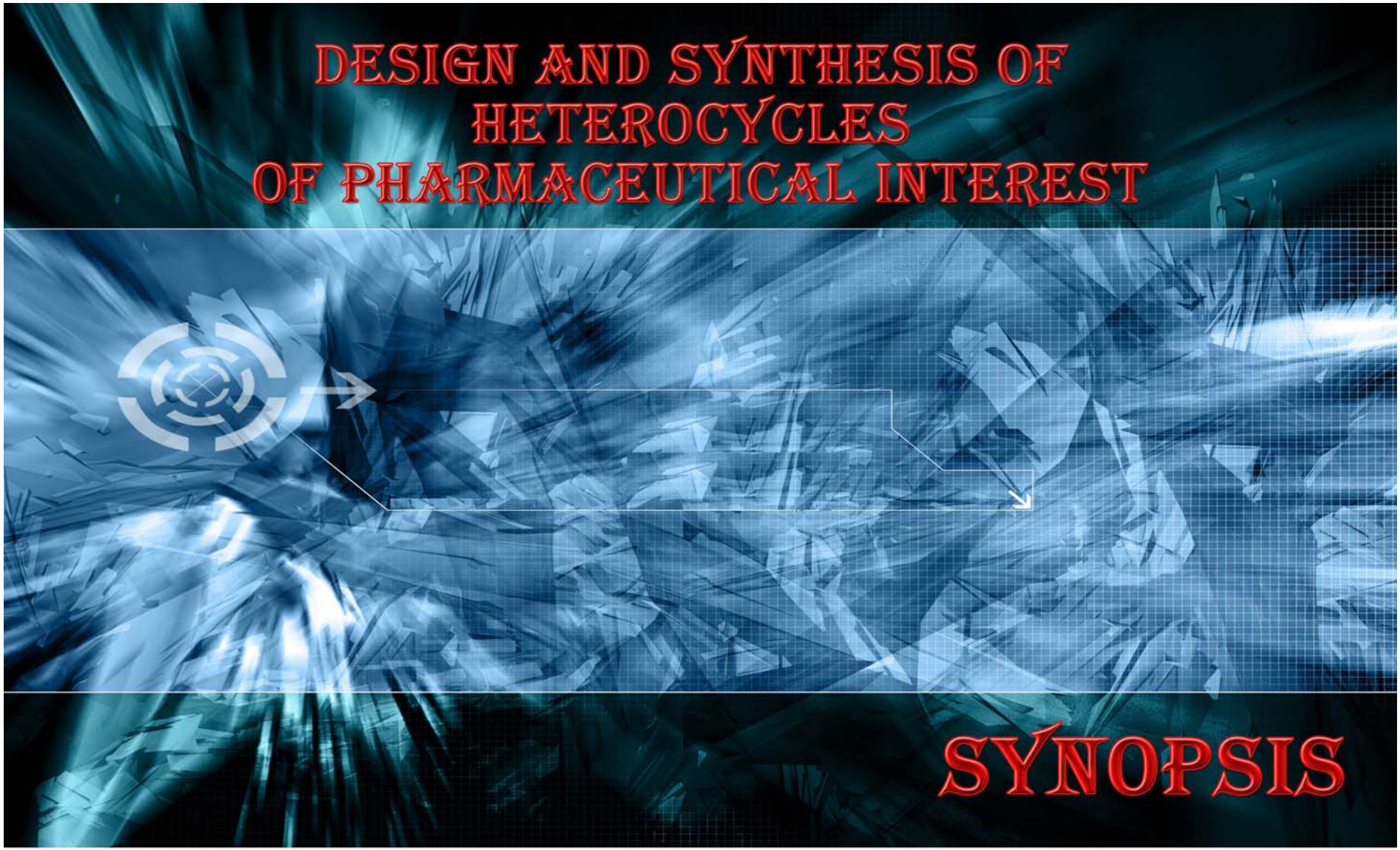
I am extremely indebted to Department of Chemistry, Saurashtra University for providing me the excellent laboratory facilities and kind furtherance for accomplishing this work. I express my grateful acknowledgement to Gujarat State Government for Junior Research Fellowship which lessened my financial worries to some extent. Finally each individual creature on this beautiful planet is created by God to fulfil a particular role. Whatever I have achieved in life is thorough His help, and an expression of His will. He showered His grace on me through some outstanding teachers and colleagues and when I pay my tribute to these fine persons. I merely praising His glory.

Nandalal V. Shekhada.

CONTENTS


DEDICATED TO
MY LOVING
PARENTS


DESIGN AND SYNTHESIS
OF HETEROCYCLES
OF PHARMACEUTICAL
INTEREST


DESIGN AND SYNTHESIS OF
HETEROCYCLES
OF PHARMACEUTICAL INTEREST
SYNOPSIS

A comprehensive summary of the work to be incorporated in the thesis entitled **"DESIGN AND SYNTHESIS OF HETEROCYCLES OF PHARMACEUTICAL INTEREST"** has been described as under.

[A] STUDIES ON PYRAZOLES

[B] STUDIES ON MICROWAVE INDUCED ORGANIC REACTION ENHANCEMENT

[A] STUDIES ON PYRAZOLES

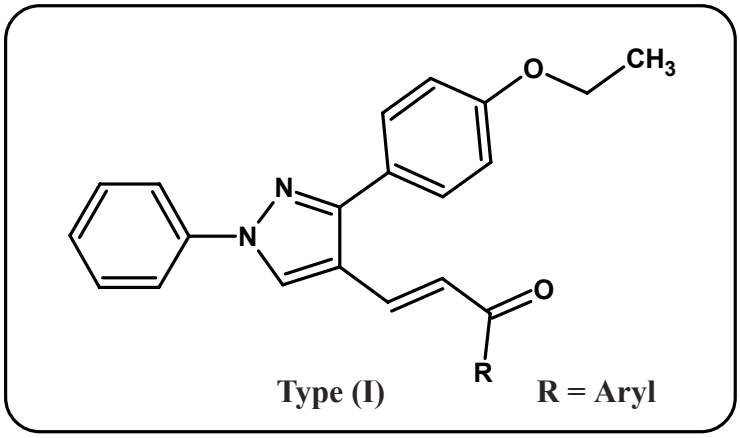
Literature survey reveals that nitrogen containing heterocyclic compounds like pyrazoles have received considerable attention in recent years due to their biological and pharmaceutical activities like antiinflammatory, antitumor, fungicidal, antitubercular, amoebicidal, herbicidal, anticonvulsant, hypnotic, CNS depressant, plant growth regulatory activity etc.

Our efforts are focused on introduction of chemical diversity in the molecular frame work in order to synthesizing active molecule of widely different composition. Prompted by these facts, we have designed and synthesized some novel chalcones, pyrazolines, arylidines, pyrimidines, cyanopyridines, cyanopyridones, isoxazoles, imidazolinones, acetonitriles and azomethines bearing pyrazole nucleus. The study is described in the following parts.

PART-I : STUDIES ON PYRAZOLINES

Pyrazoline derivatives represent one of the modest class of compounds possessing wide range of pharmacological activities like antibacterial, analgesic, anthelmintic, antiinflammatory, antitubercular etc. These valid observations led us to synthesise some novel pyrazoline derivatives bearing 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole moiety, which have been described as under.

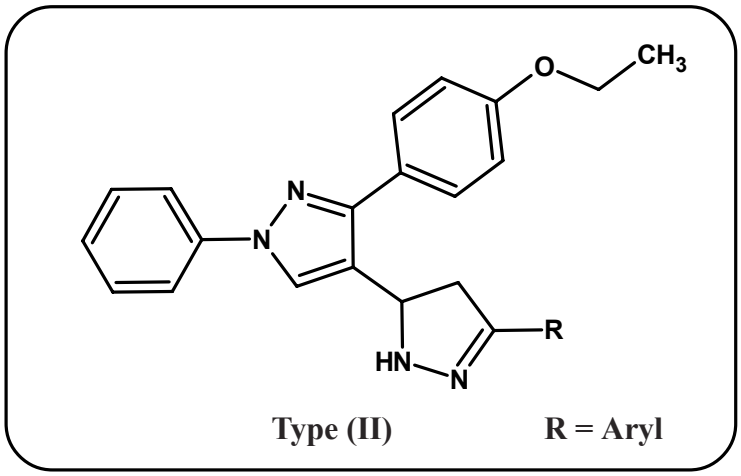
SECTION-I : Synthesis and biological evaluation of 1-Aryl-3-(1',N-phenyl-3'- *p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-ones



Type (I) **R = Aryl**

The chalcone derivatives of type (I) have been prepared by the condensation of 1,N-phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with different aryl ketones in the presence of 40% NaOH.

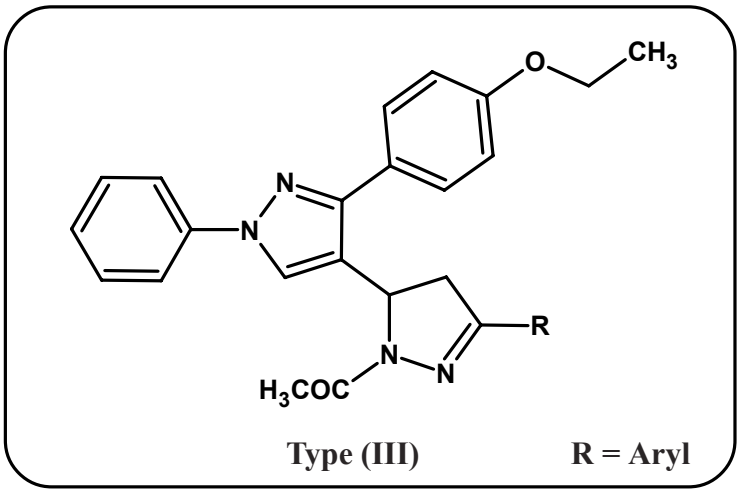
SECTION -II : Synthesis and biological evaluation of 3-Aryl-5-(1',N-phenyl -3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines



Type (II) **R = Aryl**

The pyrazoline derivatives of type (II) have been prepared by the reaction of chalcones of type (I) with hydrazine hydrate.

SECTION-III : Synthesis and biological evaluation of 1,N-Acetyl-3-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines



Type (III) **R = Aryl**

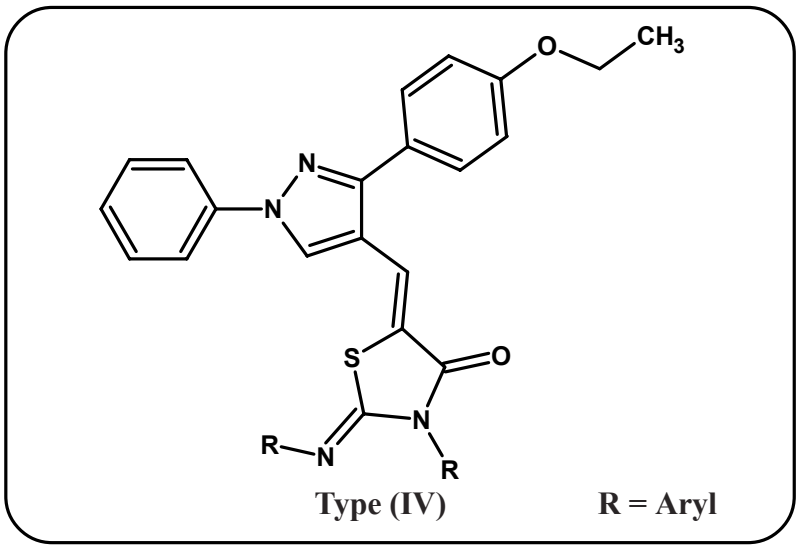
The pyrazoline derivatives of type (III) have been prepared by the reaction of chalcones of type (I) with hydrazine hydrate in glacial acetic acid.

PART-II : STUDIES ON PYRIMIDINES

The emerging role of pyrimidines in pharmaceutical chemistry as well as in biochemistry stimulated tremendous interest in the synthesis of pyrimidines with therapeutic potential.

In order to achieving better therapeutic activity, we have synthesised some new pyrimidine derivatives bearing pyrazole nucleus which is described as under.

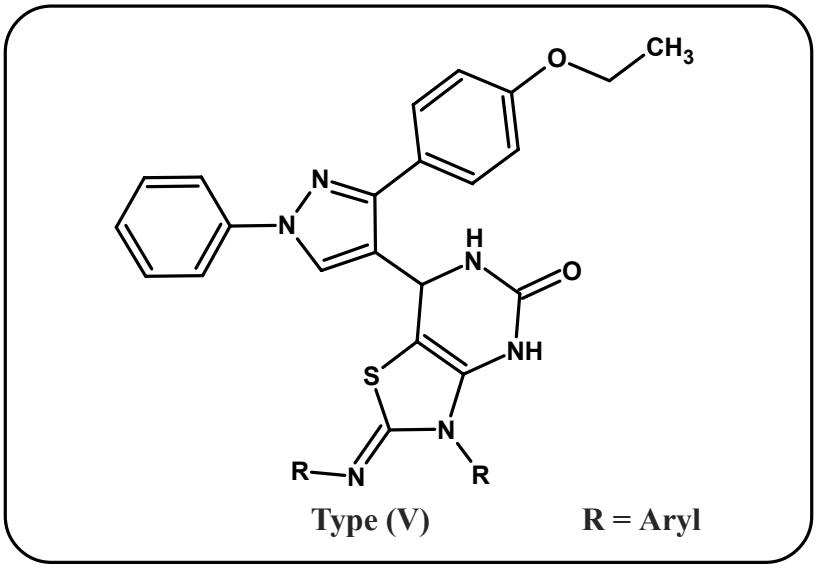
SECTION–I : Synthesis and biological evaluation of 2-Arylimino-3,N-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-4-thiazolidinones.



Type (IV) **R = Aryl**

The arylidines of type (IV) have been prepared by condensation of 1,N-phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with different thiazolidinones in glacial acetic acid.

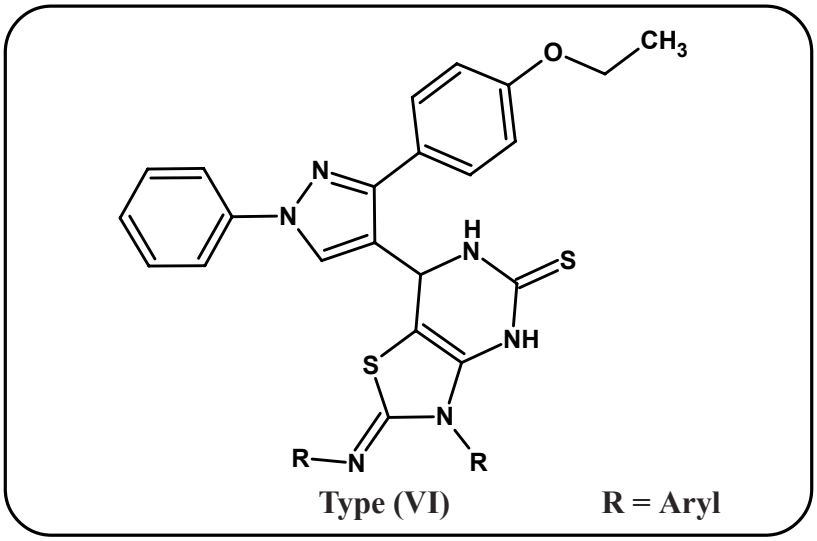
SECTION–II : Synthesis and biological evaluation of 6-Arylimino-7,N-aryl-2-oxo-4-(1',N-phenyl-3'-*p*-ethoxyphenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro thiazolidino-[4,5-e]-pyrimidines.



Type (V) R = Aryl

Pyrimidinones of type (V) have been prepared by the condensation of 2-arylimino-3,N-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-4-thiazolidinones with urea in glacial acetic acid with fused sodium acetate.

SECTION–III : Synthesis and biological evaluation of 6-Arylimino-7,N-aryl-2-thio-4-(1',N-phenyl-3'-*p*-ethoxyphenyl pyrazol-4'-yl)-1,2,3,4- tetrahydro thiazolidino-[4,5-e]-pyrimidines.



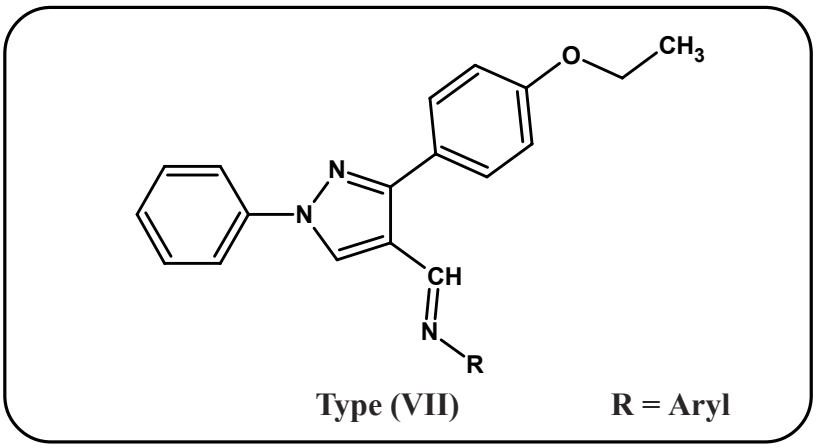
Type (VI) R = Aryl

Pyrimidinones of type (VI) have been prepared by the condensation of 2-arylimino-3,N-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-4-thiazolidinones with thiourea in glacial acetic acid with fused sodium acetate.

PART-III : STUDIES ON ARYLAMINOMETHYL DERIVATIVES

Arylaminomethyl derivatives represents one of the modest classes of compounds possessing wide range of therapeutic activities, such as antimicrobial, antimalarial and antibacterial. With a view to getting better therapeutic agents and to evaluate it's pharmacological profile, different type of azomethine derivatives and arylaminomethyl derivatives have been prepared, which have been described as under.

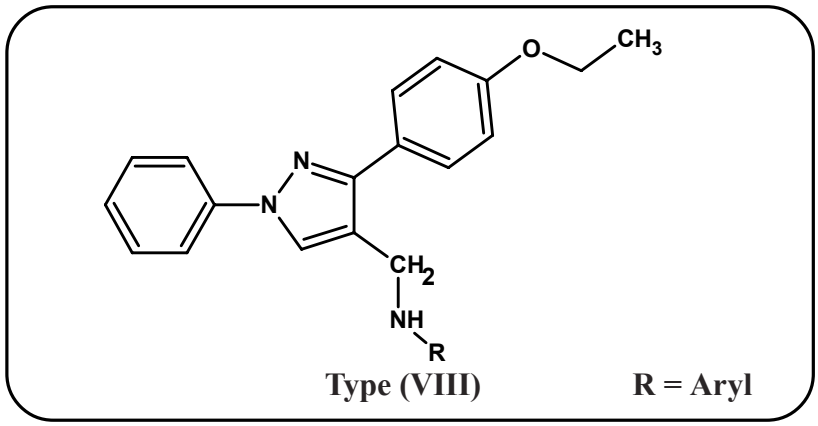
SECTION-I : Studies on N-Aryl-1,N-phenyl-3-*p*-ethoxyphenyl pyrazol-4-yl-azomethines



Type (VII) **R = Aryl**

The azomethines of type (VII) have been prepared by the condensation of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with different aromatic amines.

SECTION–II : Synthesis and biological evaluation of 4-Arylaminomethyl 1,N-Phenyl-3-*p*-ethoxyphenyl pyrazoles.



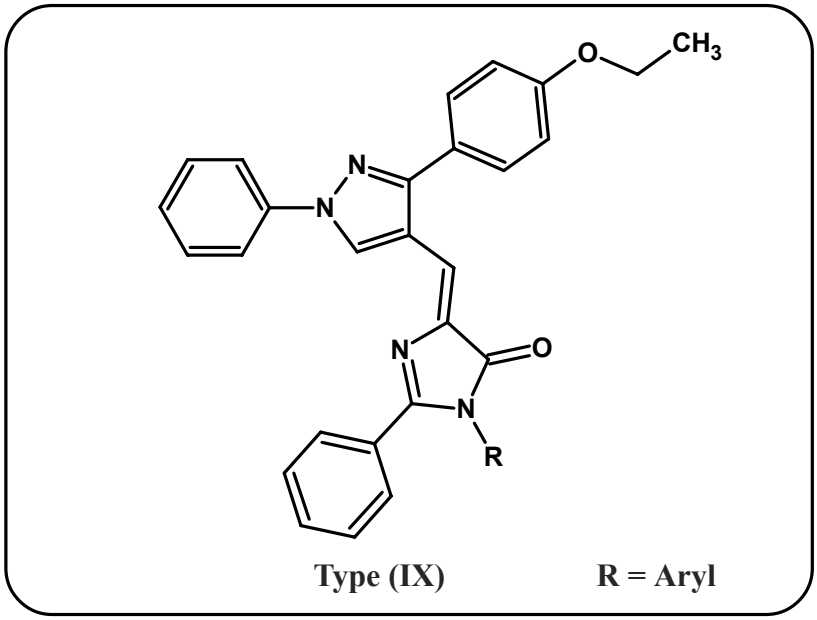
Type (VIII) **R = Aryl**

The compounds of type (VIII) have been prepared by the reaction of compounds of type (VII) with an. $NaBH_4$.

PART - IV : STUDIES ON IMIDAZOLINONES

Imidazolinone derivatives have been found to be potent drug in pharmaceutical and possess a wide range of biological activities such as anticonvulsant, antiinflammatory, hypnotic, sedative, antihistamine and antithyroid. In order to develop medicinally important compounds, we have synthesised some new imidazolinones shown as under.

SECTION-I : Synthesis and biological evaluation of 1,N-Aryl-2-phenyl-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethine)-imidazolin-5-ones



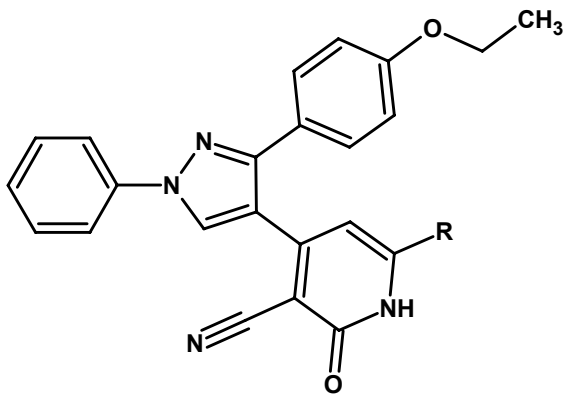
Type (IX) **R = Aryl**

The imidazolinone derivatives of type (IX) have been prepared by the reaction of azalactone with different aryl amine in pyridine.

PART - V : STUDIES ON CYANOPYRIDONES

The group of compounds containing cyanopyridone ring system have a prominent feature in medicinal chemistry and possess biological activities such as analgesic, antidiabetic, anticonvulsant, insecticidal and antibacterial etc. In view of these facts, it was contemplated to synthesise cyanopyridone derivatives which have been described as under.

SECTION - I : Synthesis and biological evaluation of 3-Cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-6-aryl-1,2-dihydro-2-pyridones.



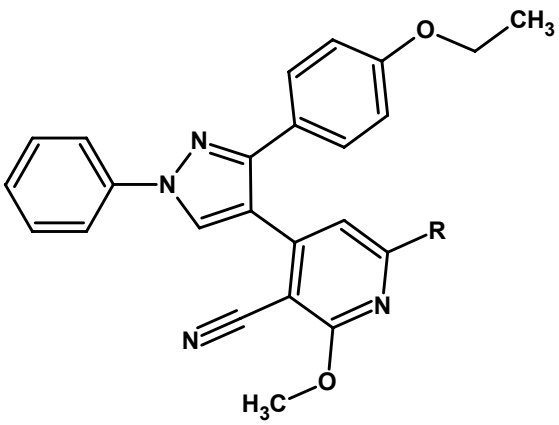
Type (X) **R = Aryl**

The cyanopyridones of type (X) have been prepared by the condensation of chalcones of type (I) with ethylcyanoacetate and ammonium acetate.

PART-VI : STUDIES ON CYANOPYRIDINES

Cyanopyridine plays a vital role owing to their wide range of biological activities such as antihypertensive, antibacterial, antidiabetic and anticholestemic. They have been also used as dyes for cotton and polyester fabrics.It appeared of interest to design and synthesise cyanopyridine derivatives, which have been described as under.

SECTION–I : Synthesis and biological evaluation of 2-Methoxy-3-cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl–pyrazol-4'-yl)-6-aryl-pyridines



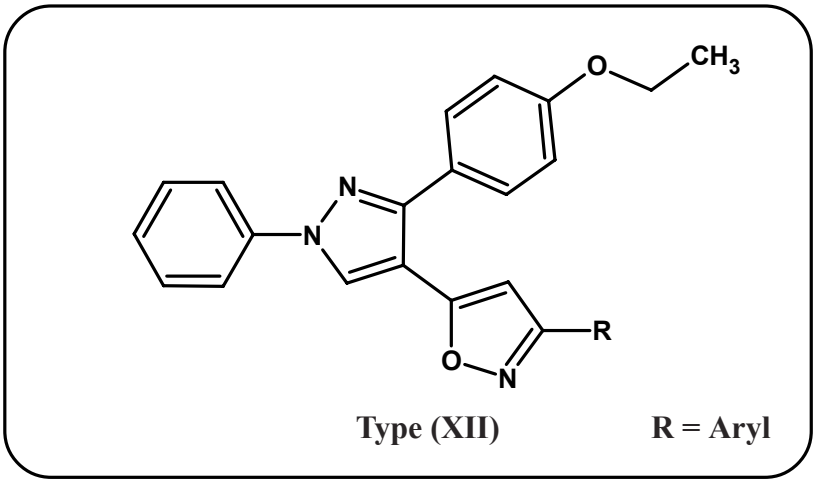
Type (XI) **R = Aryl**

2- Methoxy-3-cyanopyridines of type (XI) have been prepared by the condensation of chalcones of type (I) with malononitrile and sodium methoxide.

PART-VII : STUDIES ON ISOXAZOLES

It has been reported that isoxazole derivatives possess remarkable pharmacological importance and biological activities such as antifungal, antibacterial, sedative and hypnotics etc. In order to developing medicinally important compounds we have synthesized some new isoxazole derivatives shown as under.

SECTION - I : Synthesis and biological evaluation of 3-Aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-isoxazoles



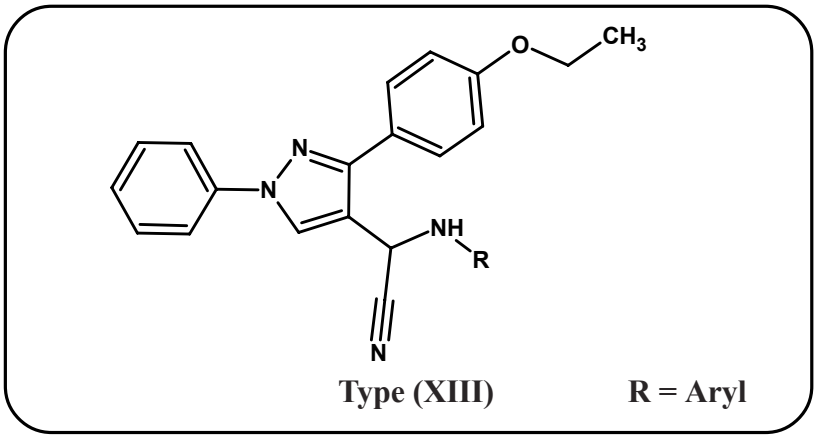
Type (XII) **R = Aryl**

The isoxazole derivatives of type (XII) have been prepared by the reaction of chalcones of type (I) with anhydrous sodium acetate and hydroxylamine hydrochloride in glacial acetic acid.

PART - VIII : STUDIES ON *a*-ARYLAMINONITRILES

Recently substituted nitrile derivatives have drawn considerable attention due to their good pharmacological activities like cardiovascular, sedative, antifungal and antibacterial. By considering these valid observations, we have synthesised some new nitriles which have been described as under.

SECTION - I : Synthesis and biological evaluation of *a*-Arylamino-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-acetonitriles.



Type (XIII) **R = Aryl**

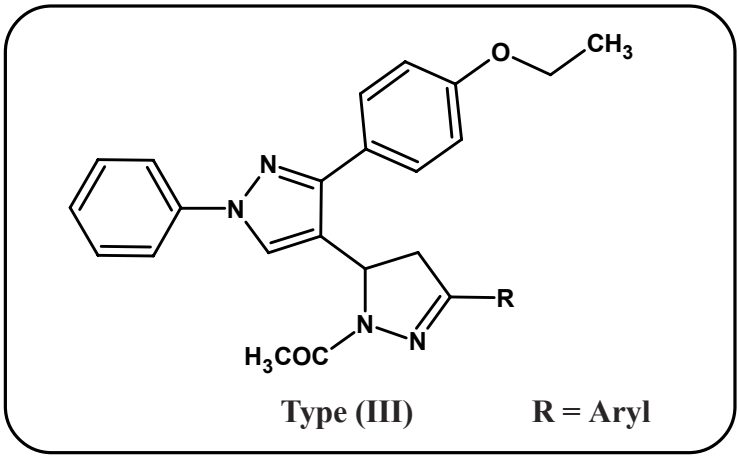
The nitriles of type (XIII) have been prepared by the condensation of 1,N-phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with different aromatic amines in presence of sodium cyanide and glacial acetic acid at 0-5 ^{0}C.

[B] STUDIES ON MICROWAVE INDUCED ORGANIC REACTION ENHANCEMENT

In the recent years, MORE (Microwave Induced Organic Reaction Enhancement) technique has become very popular due to substantial reduction in reaction time, operational time, operational simplicity and formation of clear reaction products. Keeping this in view, we investigated the synthesis of acetyl pyrazolines and cyano pyridines using microwave irradiation.

PART - I : STUDIES ON ACETYLPYRAZOLINES

SECTION -I : Synthesis and biological evaluation of 1,N-Acetyl-3-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines.

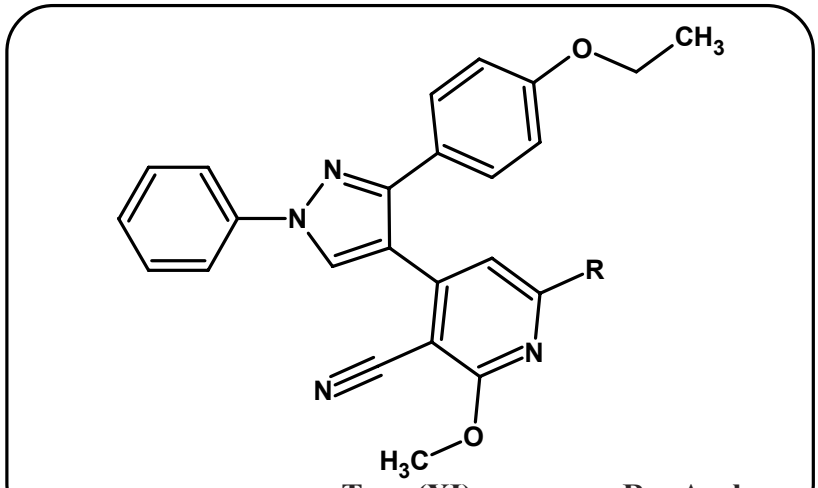


Type (III) **R = Aryl**

The pyrazoline derivatives of type (III)have been prepared by the reaction of chalcones of type (I) with hydrazine hydrate in glacial acetic acid under microwave irradiation in few minutes.The results obtained are compared with traditional synthetic method.

PART - II : STUDIES ON CYANOPYRIDINES

SECTION–I : Synthesis and biological evaluation of 2-Methoxy-3-cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl–pyrazol-4'-yl)-6-aryl-pyridines



Type (XI) R = Aryl

2- Methoxy-3-cyanopyridines of type (XI) have been prepared by the condensation of chalcones of type (I) with malononitrile and sodium methoxide under microwave irradiation in few minutes. The advantages of microwave synthesis has been reported.The results obtained are compared with traditional synthetic method.

CHARACTERISATION :

The constitution of newly synthesised products have been supported by using elemental analyses, Infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

***In vitro* study on multiple biological activities :**

(i) All the compounds have been evaluated for their antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 mg. The biological activity of the synthesised compounds have been compared with standard drugs.

(ii) Selected compounds have been evaluated for their ***in vitro*** biological assayv like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 mg/ml using Rifampin as a standard drug,which have been tested by Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), Alabama,U.S.A.

Signature of Guide
Dr. (Mrs.) H. H. Parekh

Signature of Candidate
(Nandalal V. Shekhada)

INTRODUCTION

Research in the field of pharmaceutical has its most important task in the development of new better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparation which are new and original. In addition to these objectives, we may search for newer drugs which exhibit some clear advantages over a drug already known. Such advantages may be qualitative or quantitative improvement in activity, the absence of undesirable side effects, lower toxicity, improved stability or decreased cost.

The word 'drug' is derived from the French word 'drogue' which means a dry herb. According to "WHO" a drug may be defined as "any substance or product which is used or intended to be used for modifying or exploring physiological system or pathological status for the benefit of recipient".

In the nineteenth century, chemistry was developed as a science, both in terms of experimental procedures and scientific theory. Scientist isolated and purified single compounds from natural extracts. Method of organic synthesis were developed that helped chemists altering structures in a predictable way.

Chemistry related with pharmaceutically important compounds is mainly divided in two parts. The first, chemotherapy, concerns the treatment of infections, parasites or maligant diseases by chemical agents, usually substances that shows selective toxicity towards the pathogen. The other division relates to diseases of bodily disfunction and the agents employed are mainly compounds that effect the functioning of enzymes, the transmission of nerve impulses or the action of hormones on receptors.

A prerequisite for the design of safe drugs is knowledge about the various metabolic reactions that xenobiotics and endogenous compounds undergo in the organism. Because pharmacological activity depends on molecular structure, the medicinal chemist is restricted in the choice of functional groups for the design of new drugs. Often he

finds or she encounters a situation where a structure has adequate pharmacologic activity but has an inadequate pharmacokinetic profile (i.e., absorption, distribution, metabolism and excretion). This is because pharmacology and pharmacokinetic departments in the pharmaceutical industry often do not collaborate at the early stage of drug development. It is only later, when the new compound is tested in animals or in humans, that pharmacokinetic disadvantages become obvious.

A large number of important drugs have been introduced during the period of 1940 to 1960. This perod is known as 'Golden Period' of new drug discovery. Thus starting from 1933-the first antibacterial drug prontosil leading to various sulpha drugs; 1940-penicillin, antibiotics; 1945-chloroquine, antimalarial;1957-chlorthiazide, diuretic; 1958-adrenergic beta blockers coronary vasodilatory; 1960-semi synthetic penicillin, antibacterial1965- trimethoprim, antimicrobial; 1967-disodium chromoglycoate, antiallergic; 1972-cimetidine, H2-antagonist; 1975-verapamil, calcium antagonist;1981-captopril,antihypertensive. These are some specific examples representing new therapeutics

Modern drug discovery starts with the identification of a pharmacologic target that is hypothetically the primary cause of disease. Potential targets include host cell genes, receptors, signaling systems, organelles and biochemicals such as enzymes. Additionally, an element of a disease modifying process, such as an inflammatory mediator, may be a target. Biological processes required for propagation of infectious agents have also proven to be therapeutically useful targets; examples include protease and reverse transcriptase of the human immuno deficiency virus(HIV). Common to all targets selected as therapeutic opportunities is the hypothesis that some type of pathogenetic linkage exists to the disease- causing process, rather than to specific signs, symptoms or effects.

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provides false synthons in biosynthetic process or block the normal functioning of biological receptors. The inhibition of amide resonance

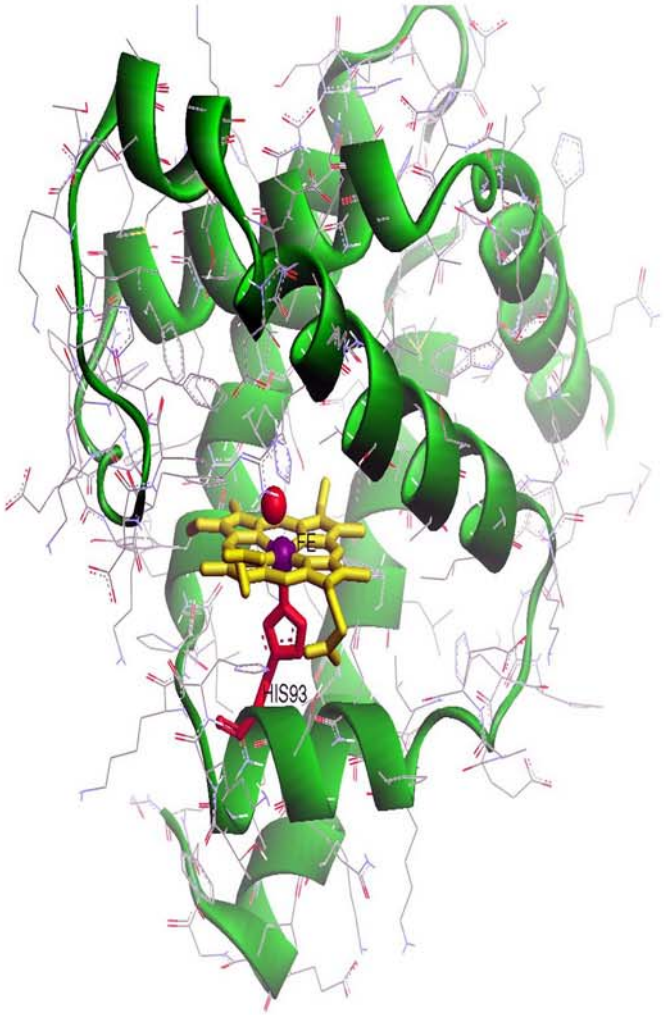
resulting into more susceptibility of b-lactam to nucleophile is considered at least in part responsible for antibacterial property, apparently by acetylating transpeptidase and thus inhibiting bacterial cell wall biosynthesis.

Most of the alkaloids which are nitrogenous bases occurring in plants and many antibiotics including penicillin and streptomycin have also heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and anthocyanin are heterocycles. Most of the sugars are their derivatives including Vitamin C for instance, exist largely in the form of five membered. Vitamin B6 (Pyridoxine) is a derivative of pyrimidine essential in aminoacid metabolism. .

Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing pyrazole nucleus. The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesized products for their pharmacological profile against several strains of bacteria and fungi.

AIMS AND OBJECTIVES

- To generate several derivatives like chalcones, pyrazolines, cyanopyridines, cyanopyridones, thiazolidinones, pyrimidines, imidazolines, arylaminomethyl derivatives, acetonitriles bearing pyrazole nucleus. bearing pyrazolemoiety.
- To synthesise biologically active pyrazolines and methoxy pyridines using microwave induced synthesis method.
- To characterize these products for structure elucidation using spectroscopic technique like IR, PMR and Mass spectral studies.
- Purity of all compounds have been checked by thin layer chromatography.
- To evaluate these new product for better drug potential against different strain of bacteria, fungi and for antitubercular activity against ***Mycobacterium Tuberculosis*** **H_{37}Rv.**



{A}

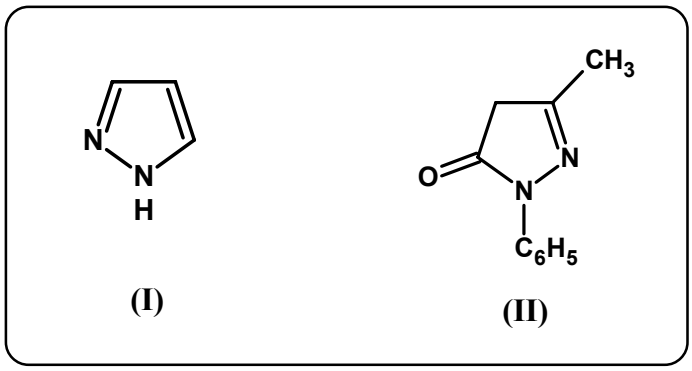
STUDIES ON PYRAZOLES

INTRODUCTION

Pyrazoles are well known five membered heterocyclic compounds which consist of a doubly unsaturated five membered ring (I)containing two adjacent nitrogen atoms.Knorr[1] introduced the name pyrazole for these compounds to donate that the nucleus was derived from pyrrole by replacement of carbon by nitrogen

Considerable interest has been focused on the pyrazoles derivatives which has been known to possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsunt and antihypertensive activities.The discovery of this class of drugs provides an outstanding case history of modern drug development and also point out the unpredictability of biological activity from structural modifications of a prototype drug molecule.

The knowledge of such applications has pointed out that N-substituted pyrazoles are important targets to be prepared. Knorr[2,3] first synthesized a compound containing this system in 1883 by a reaction of ethylaceto acetate with phenylhydrazine which yielded 1-phenyl-3-methyl-5-pyrazolone (II).



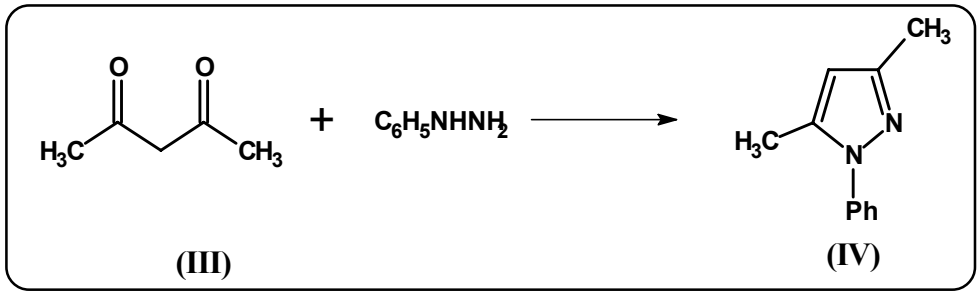
(I) **(II)**

since many drugs and dyes contain the pyrazole nucleus, the class has been widely studied and the field continues to be active today.

SYNTHETIC ASPECTS

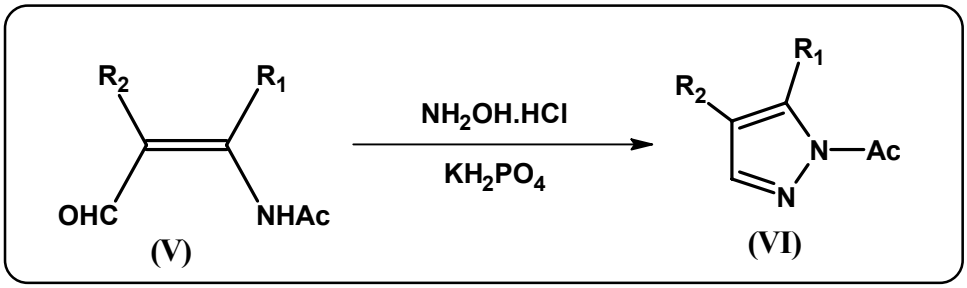
Various methods for the preparation of pyrazoles have been cited in literature.

1. The reaction of hydrazine or its derivatives such as alkyl or aryl hydrazines, semicarbazine or aminoguanidine with 1,3-dicarbonyl compounds is well known..



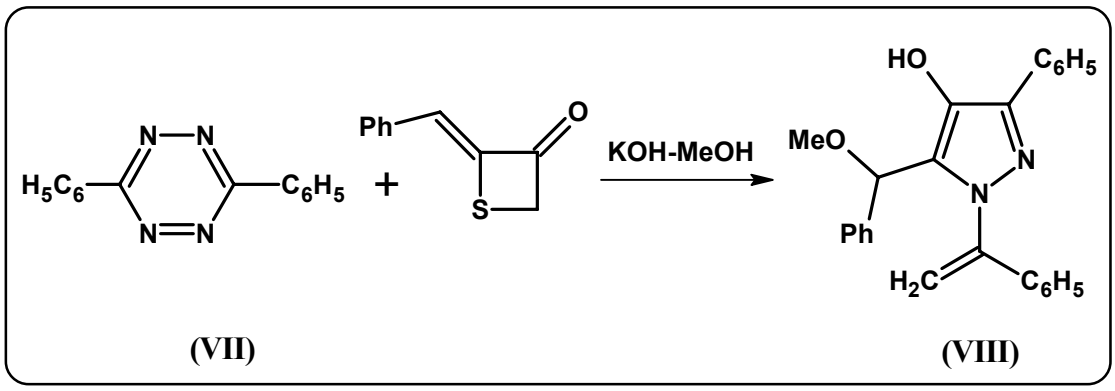
(III) (IV)

2. R. C. Boruah[4] et. al. suggested one pot synthesis of pyrazoles from-b-formyl enamides.



(V) (VI)

3. M. J. Kurth[5] et. al. suggested a novel route for synthesis of fully substituted 1H-pyrazoles.

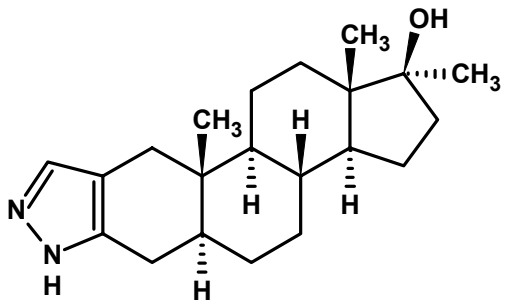


(VII) (VIII)

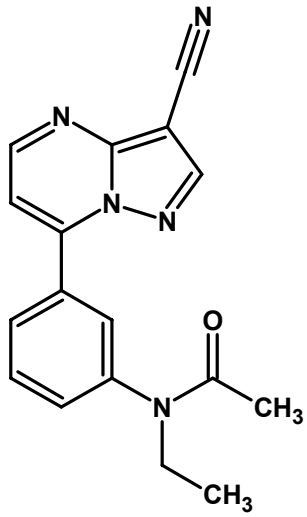
4. The reaction of hydrazines with a,b-unsaturated carbonyl compounds.
5. The reaction of aliphatic diazo compounds such as diazomethane or diazoester with acetylene or olefins.

THERAPEUTIC IMPORTANCE

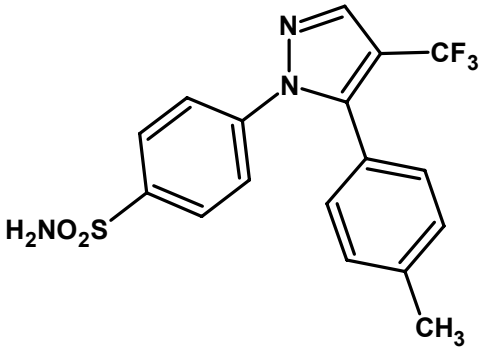
Pyrazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having pyrazole nucleus with good pharmacological activitiesare listed below.



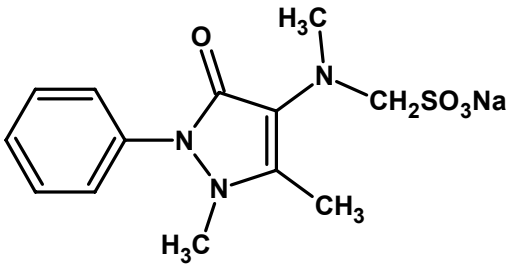
Stanozolol
(Insecticide)



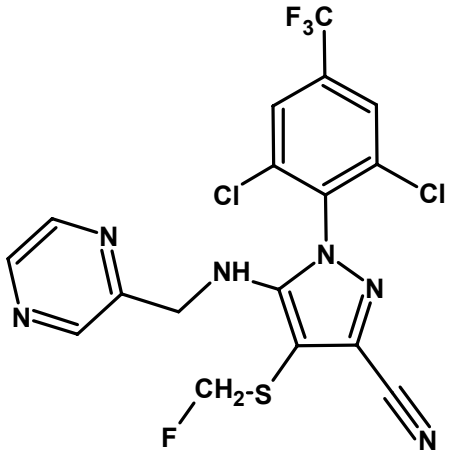
Zaleplon
(Sedative, Hypnotic)



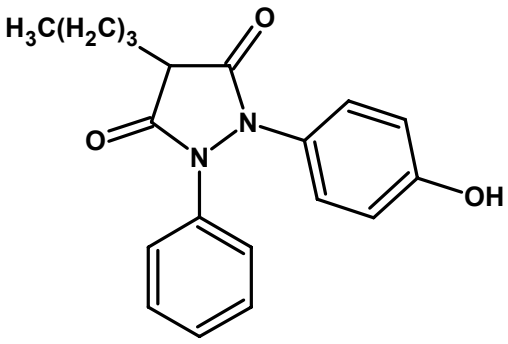
Celecoxib
(Antiinflammatory)



Novalgin
(Antipyretic, Analgesic)



Pyrafluprole
(Insecticide)



Oxyphenbutazone
(Antiarthritic)

Much research has been carried out with the aim to finding therapeutic values of pyrazole moiety since their discovery. A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like,

(a) Antiinflammatory[6-7]

(b) Insecticidal[8-9]

(c) p-38 Kinase inhibitors[10]

(d) Antiepileptic[11]

(e) Nematicidal[12]

(f) Antitumor[13]

(g) Anticancer[14]

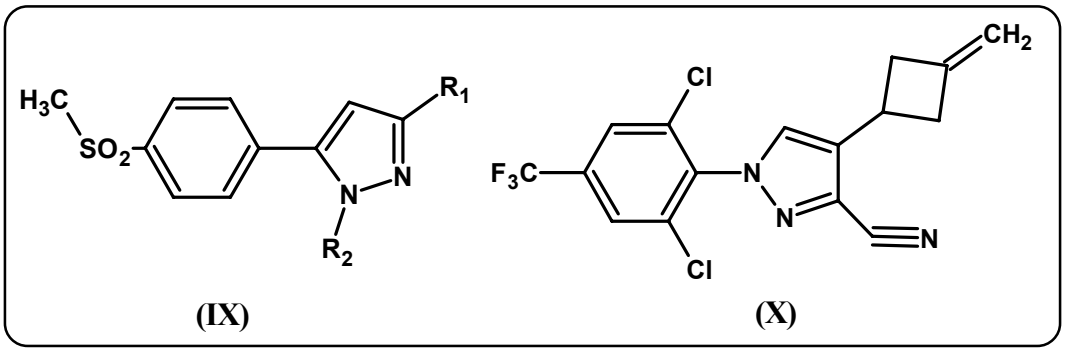
(h) Antiviral[15]

(i) Herbicidal[16]

(j) AntiHIV[17]

Jansen Karte et al.[18] have synthesized pyrazole derivatives as pesticides. Somega Shinzo and co-workers[19] have synthesized pyrazole derivatives and reported their herbicidal activity. Geheing Reinhald et al.[20] have synthesized 5-amino-4-cyano-1-aryl-pyrazoles and shown them as plant growth inhibitors. Nakamura Katsyga and co-workers[21,22] have prepared 1,5-diphenyl pyrazoles as Cox-2-inhibitors (IX).

Bernard Banks et al.[23] have synthesized pyrazole derivatives (X) and tested for their antiparasitic activity.



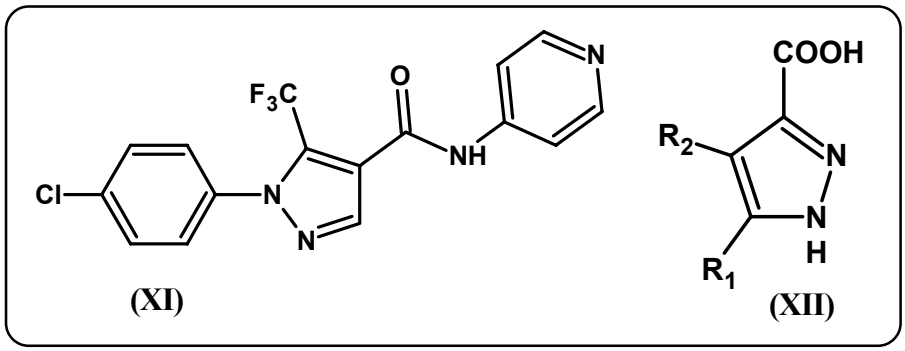
Menozzi G. and co-workers[24] have synthesised a series of N-substituted 4-carboxy-1-phenyl-lH-pyrazole-5-propanamides, in which some of the compounds showed a platelet antiaggregating activity *in vitro* superior or comparable to that of acetylsalicylic acid, as well as moderate antiinflammatory, analgesic and antipyretic activities on rats or mice. Several new 1-methyl-5-[substituted-4-oxo-1,2,3-benzotriazin-

3-yl]-1*H*-pyrazole-4-acetic acids and their ethyl ester derivatives were prepared by Giuseppe Daidone[25] and tested for analgesic and antiinflammatory activities, acute toxicity, ulcerogenic effect, and *in vitro* inhibitors of 3a-hydroxysteroid dehydrogenase (3a-HSD) . Ejima Akio et. al.[26] have synthesized pyrazole derivatives as antitumor agents.

Laborde Edgardo et al.[27] have found that pyrazoles possess glycine transporter-2-inhibitor activity. Andrew Thurkaub et al.[28] have synthesized high affinity C5a receptor modulator pyrazoles. Nagaaki Sato et. al.[29] have prepared arylpyrazole derivatives and evaluated as neuropeptide Y5 receptor antagonist. One of the compound with chiral 2,3-dihydro-1H-cyclopenta[a]naphthalene moiety, showed good binding affinity and antagonistic activity for the Y5 receptor. G. M. Hi Yamanonch[30] has prepared pyrazoles as glycine transporter protein inhibitors.

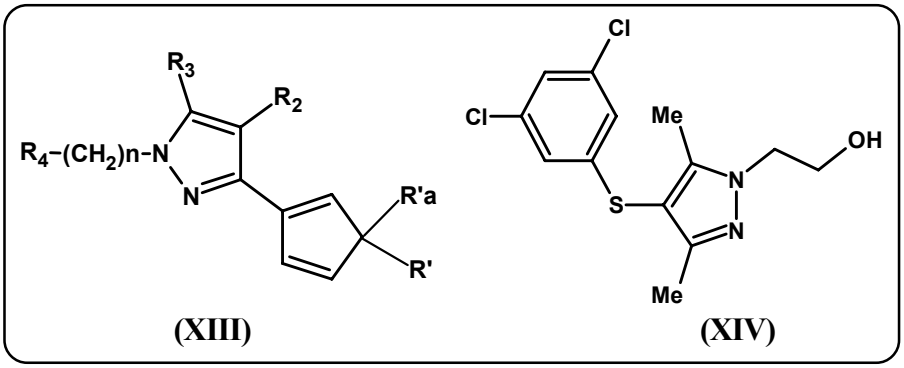
David L. S. et al[31] have reported pyrazoles as activators of the nitrile oxide receptor and soluble guanglate cyclase agent. T Van Herk et al.[32] have demonstrate pyrazoles as nicotinic acid receptor (XI). Barber Christopher et al.[33] have synthesized pyrazole derivatives as phosphodiesterase inhibitors.

Recently, Atkinson R. N. et al.[34] have synthesized pyrazoles as sodium channel Blocker (XII). Gellibert Francoise et al.[35] have prepared pyrazole derivatives as TGF-13 inhibitors.

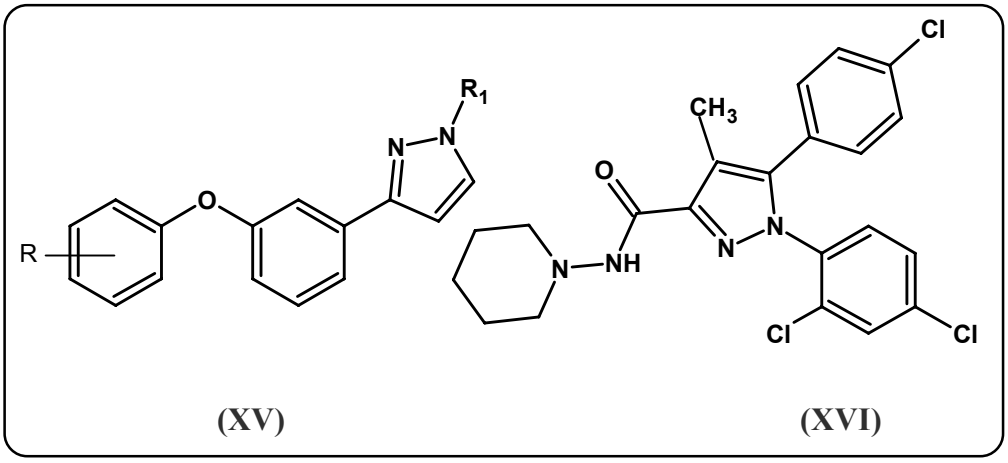


Grazid Mamalo et al.[36] have newly synthesized pyrazole derivatives tested for antimicrobial activity. R. Y. Huang and co-workers[37] have prepared some 1,2,4- triaryl-4-alkyl-pyrazoles as estrogen receptor. C. Vittoria and co-workers[38] have prepared some pyrazoles as adenosine receptor antagonists.

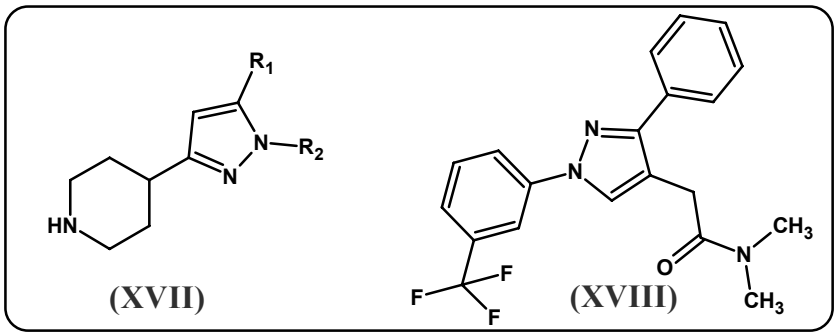
Schindler Ursula et al.[39] synthesized new pyrazole derivatives (XIII) as cardiovascular agents. Carbau Romuald and co-workers[40] have prepared pyrazole derivatives (XIV) useful as reverse transcriptase inhibitors for the treatment of HIV infection.



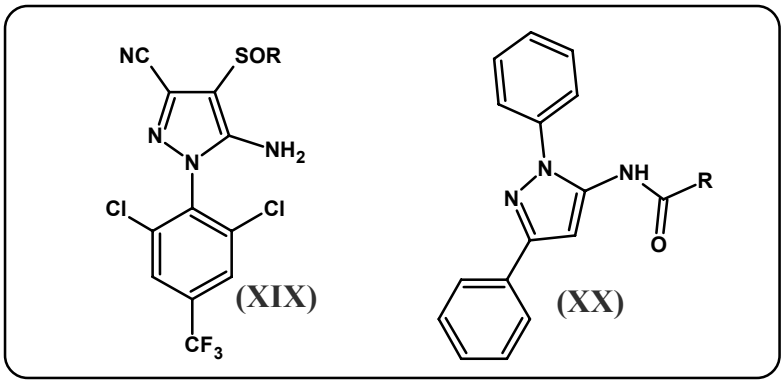
Ji Yang et al.[41] have documented 3-(4-phenoxyphenyl)pyrazole derivatives (XV) for their Sodium Channel Blockers. Ruoxi Lan et al.[42] have prepared pyrazole derivatives as Cannabinoid receptor antagonist.(XVI)



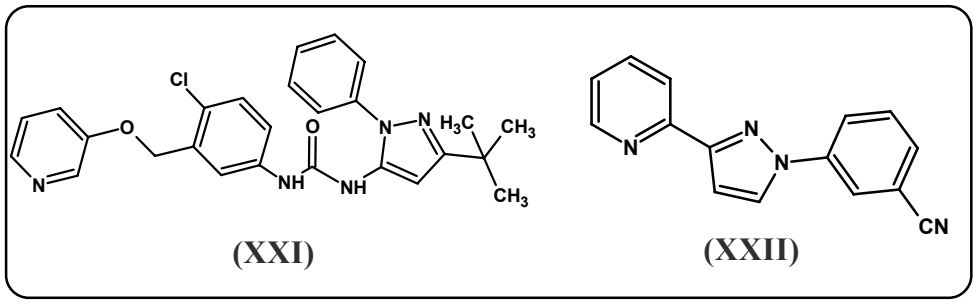
Akihiko Tanitame and co-workers[43] have synthesized new pyrazole derivatives and found that 5-[(E)-2-(5-chloroindol-3-yl)vinyl]pyrazole possesses potent antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Many of the synthesized pyrazole derivatives were potent against clinically isolated quinolone or coumarin-resistant Gram-positive strains. Gregory R. Bebernitz et al.[44] have described 1,3-diaryl-[1H]-pyrazole-4-acetamide as antidiabetic agents (XVIII). Franco chimenti, Adriana Bolasco et al.[45] have synthesized pyrazole derivatives as Monoamine Oxydase Inhibitors.



Abdel-Rahman Farghaly and Hussein el-Kashef et al.[46] have prepared pyrazole derivatives as antibacterial and antifungal agent. Pierluigi Caboni et al.[47] have reported phenylpyrazole insecticide photochemistry, metabolism and gabaergic action(XIX). Craig W. Lindsley et al.[48] have discovered positive allosteric modulators for the Metabotropic Glutamate Receptor from a series of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamides that potentiate receptor function *in vivo*(XX).



Adrian l. Gill and Martyn Frederickson et al.[49]have identified pyrazoles as a novel p38a MAP kinase inhibitors(XXI). Jeffrey roppe et al.[50]have discovered novel heteroaryl azoles that are metabotropic glutamate receptor antagonists with anxiolytic activity(XXII)



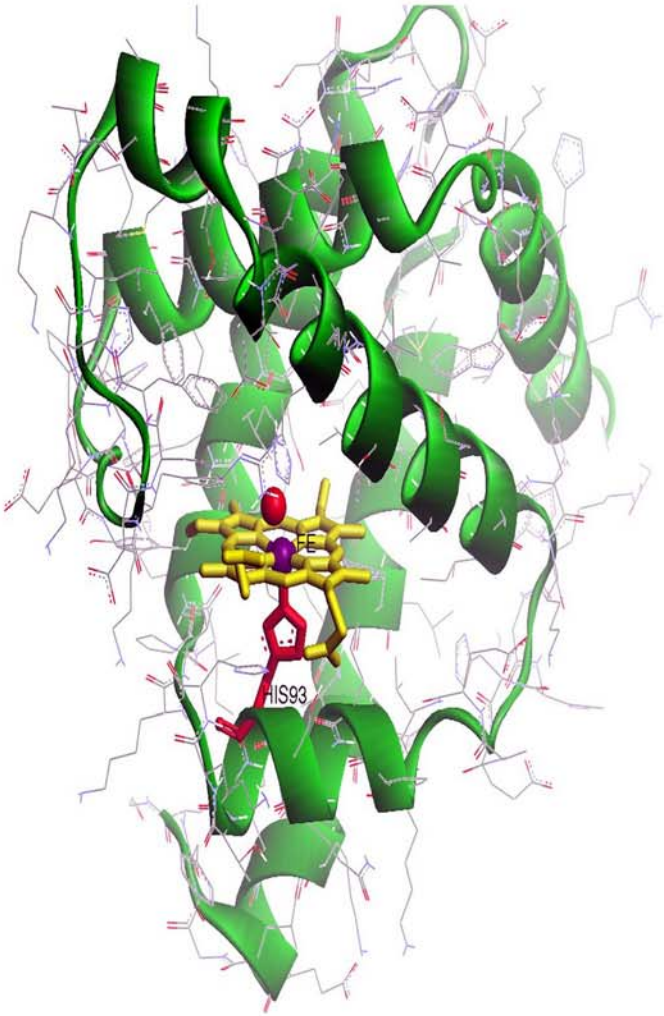
Recently, Bantwal Holla and co-workers[51] have synthesised pyrazole derivatives as potential antimicrobial agents. Antimalarial activity of 4-(5-trifluoro

methyl-1*H*-pyrazol-1-yl)-chloroquine analogues has been evaluated *in vitro* against a chloroquine resistant *Plasmodium falciparum* clone by Antoniana U. Krettli et. al.[52]. Pyrazole derivatives with nanomolar activity in the biochemical assay and able to efficiently inhibit CDK2-mediated tumor cell proliferation have been obtained by Paolo Pevarello et. al.[53].

Literature survey reveals that the compounds bearing pyrazole moiety possess potential drug activity. Looking to the diversified biological activity, it appeared of interest to synthesize some chalcones, pyrazolines, arylidines, pyrimidines, cyanopyridines, cyanopyridones, isoxazoles, imidazolinones, acetonitriles and arylaminomethyl bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance. These studies are described in following parts.

[A] STUDIES ON PYRAZOLES

PART - I : STUDIES ON PYRAZOLINES
PART - II : STUDIES ON PYRIMIDINES
PART - III : STUDIES ON ARYLAMINOMETHYLDERIVATIVES
PART - IV : STUDIES ON IMIDAZOLINONES
PART - V : STUDIES ON CYANOPYRIDONES
PART - VI : STUDIES ON CYANOPYRIDINES
PART - VII : STUDIES ON ISOXAZOLES
PART - VIII : STUDIES ON *a*-ARYLAMINONITRILES

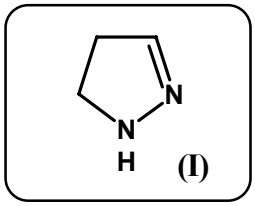


PART-I

STUDIES ON PYRAZOLINES

INTRODUCTION

Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful frame work for biological activities. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. In 1967 Jacobe, reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic behavior[1] and industrial applications.[2]

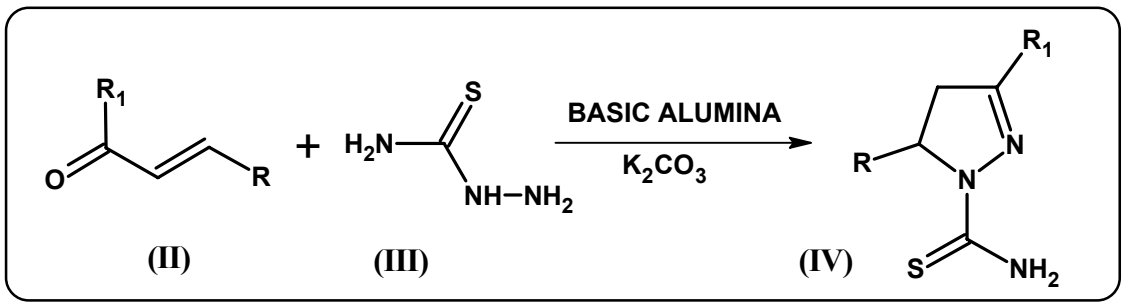


(I)

SYNTHETIC ASPECTS

Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

1. 2-Pyrazolines can be synthesized by the cycloaddition of diazomethane to substituted chalcone.[3]
2. 2-Pyrazoline can be prepared by the condensation of a, b-unsatured ketone and thiosemicarbazide in the presence of basic alumina and K_2CO_3.[4]



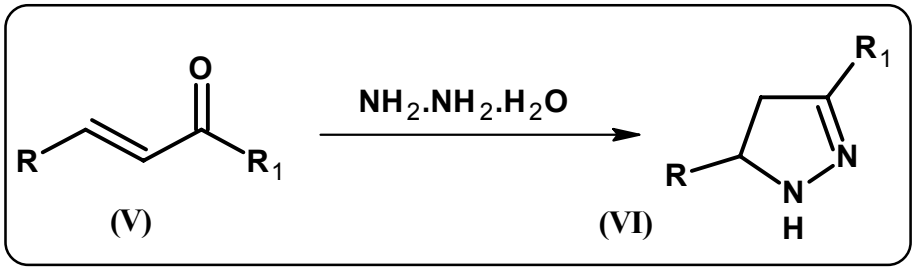
(II) (III) (IV)

3. Dipolar cycloaddition of nitrileimines of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yielded the corresponding pyrazolines.[5]

4. Epoxidation of chalcones with epoxy ketones on reaction with hydrazine hydrate and phenyl hydrazine to give pyrazolines.[6]

5. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazine.[7]

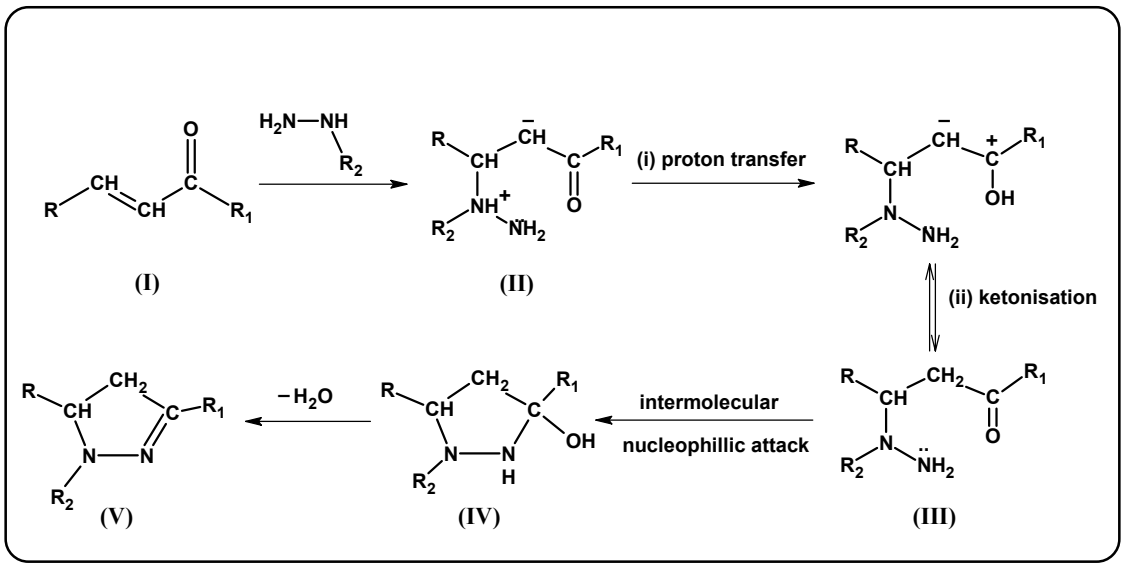
6. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate.[8]



Furthermore, B. Gyassi et al.[62] have investigated one pot synthesis of some pyrazolines in dry media under microwave irradiation. S. Paul et. al.[63] and Dandia Anshu et. al.[64] have also described the microwave assisted synthesis of 2-pyrazolines.

MECHANISM

The following mechanism seems to be operable for pyrazoline by the condensation of chalcones with hydrazine hydrate.[65]



Nucleophillic attack by hydrazine at the b-carbon of the a,b-unsaturated carbonyl system forms species (II), in which the negative charge is mainly accommodated by the electronegative oxygen atom.

Proton transfer from the nitrogen to negative oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophillic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads to carbonyl amine (IV).The later with a hydroxy group and amino group on the same carbon lose water molecule to yield the pyrazolines.

THERAPEUTIC IMPORTANCE

From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents. Some of the activities are mentioned below.

(a) Antiallergic[13]

(b) Anticonvulsant[14,15]

(c) Antidiabetic[16]

(d) Antiinflammatory[17]

(e) Antitumor[18]

(f) Antineoplastic[19]

(g) Analgesic[20,21]

(h) Bactericidal[22,23]

(i) Cardiovascular[24]

(j) Diuretic[25]

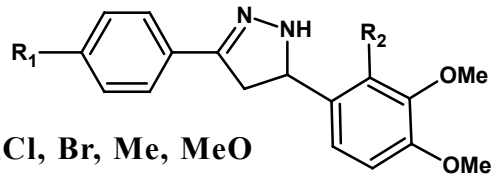
(k) Fungicidal[26]

(l) Herbicidal[27]

(m) Hypoglycemic[28]

(n) Insecticidal[29]

Shivnanda M. K. and co-workers[83] have prepared pyrazolines and reported their antibacterial activity. E. Palska et al.[84] have prepared 3,5-diphenyl-2-pyrazolines (VII) and cited their antidepressant activity.

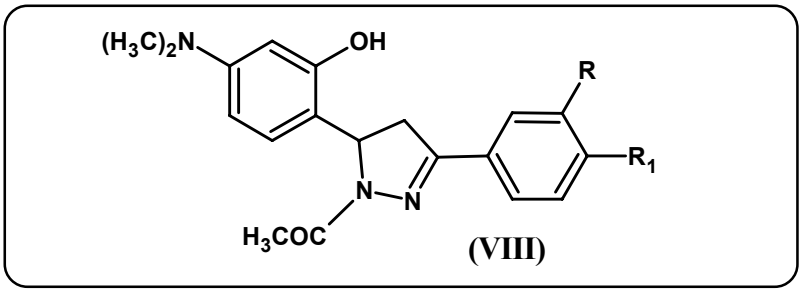


R_1 = H,Cl, Br, Me, MeO

R_2 =H, Cl

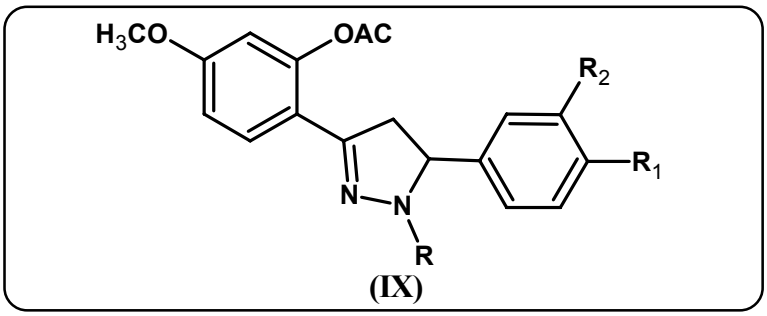
(VII)

Moreover, F. Manna and coworkers[85] have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazolines (VIII) and its derivatives which acts as potent antiinflammatory, analgesic and antipyretic agents.



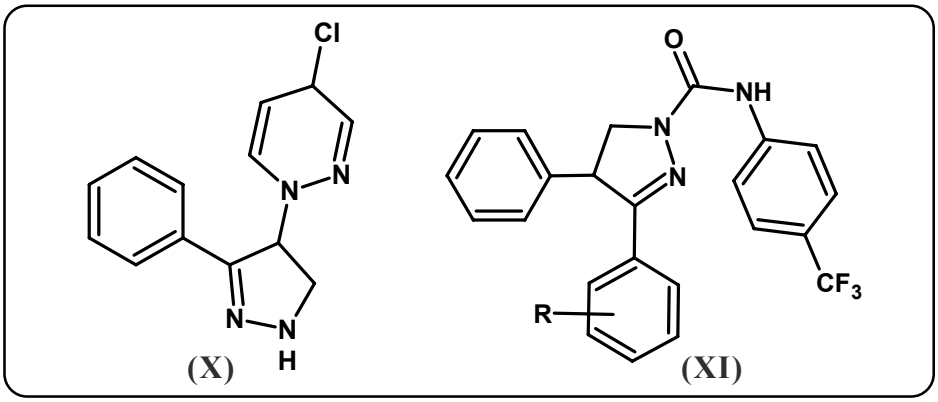
(VIII)

S. S. Sonarc et al.[86] have synthesized 3-(2-acetoxy-4-methoxyphenyl)-5-(substituted-phenyl)-pyrazolines (IX) and tested their antimicrobial activity. V. V. Fernandes et al.[87] have also synthesized some new pyrazolines as an antimicrobial agent.



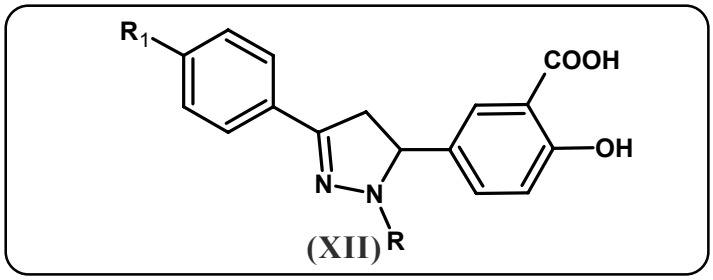
(IX)

Udupi R. H. and Bhatt A. R.[88] have reported the synthesis and biological activity of Mannich bases of certain 1,2-pyrazolines. Nugent Richard[89] investigated pyrazolines bis phosphonate ester as novel antiinflammatory and antiarthritic agent. Furthermore, Fuche Rainer et al.[90] have prepared some new 1H-pyrazoline (X) derivatives and reported them as pesticides. Tsuboi et al.[91] have synthesized some new phenylcarbonyl pyrazolines (XI) as an insecticides and at 40% concentration shows 100% mortality of spodopetra litura larve after seven drops.



(X) (XI)

Tuntawy Atif and coworkers[92] have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agent. Almstead J. et al.[93] have prepared pyrazolines as vascularization agent. G. N. Mishirika et al.[94] have also prepared 2-pyrazolines of salicylic acid (XII) possessing antimicrobial properties.

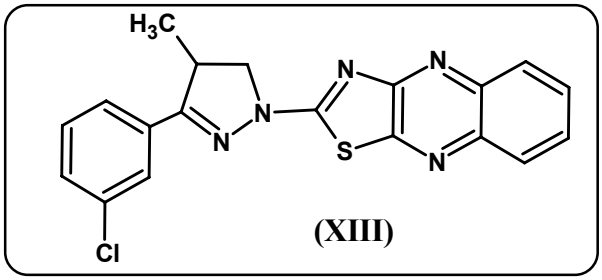


(XII)

Maurer Fritz et. al.[95] have synthesized pyrazolyl pyrazolines. In spodoptera frugiperda pesticide studies with Brassica oleracea, at 500 ppm some of compounds exhibited 100% mortality after seven days and some of compounds were claimed to be useful as pesticidal coating material agents.

Gokhan N. et al.[96] have synthesized the pyrazoline derivatives of 1-N-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines as MAO inhibitors. Matysiak J. et al.[97] have reported some novel pyrazoline derivatives as antimycotic activity of N-azolyl-2,4-dihydroxythiobenzamides. Tabarelli Z. et. al.[98] have prepared some pyrazole derivative showing activity of antinociceptive effect of novel pyrazolines in mice. Tae-Sook Jeong et. al.[99] have reported pyrazole as low-density lipoprotein (LDL) oxidation inhibitor . One of the compound was 6-fold more potent than probucol in the TBARS assay.

B. Bizzarri et. al.[100] have reported *in vitro* selective anti-helicobacter pylori activity of pyrazoline derivatives. Mohammad Abid and Amir Azam[101] have synthesized 1-N-substituted cyclised pyrazoline of thiosemicarbazones (XIII) and reported as antiamoebic activity.

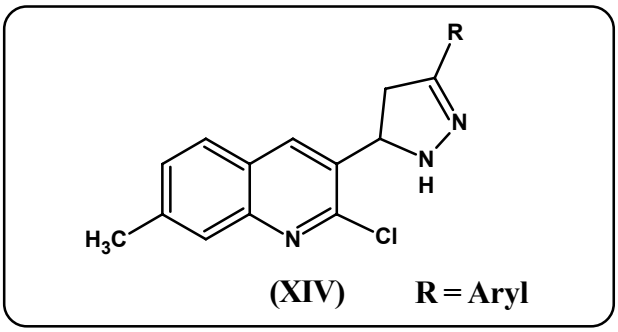


(XIII)

CONTRIBUTION FROM OUR LABORATORY

S. D. Sorthiya et. al.[102] have synthesised and tested the antimicrobial activity of *p*-(2',5'-Dibromobenzenesulphonamido)-phenyl-5-aryl-1H/acetyl/phenyl-2-pyrazolines. Parekh et. al.[103] have prepared 1-acetyl-5-aryl-3-[3-(3,4-dihydro-2-methyl-4-one-3-quinazolinyl)-phenyl]-2-pyrazolines which possess antimicrobial activity.

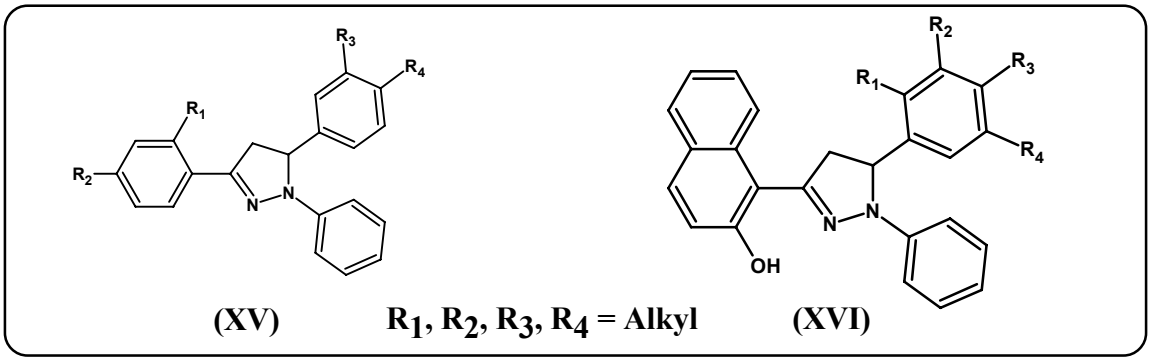
Parikh et. al.[104] have synthesised some antimicrobial pyrazolines. Tejas Upadhyay et. al.[105] and Sohit Rajvaidya et. al.[106] have prepared pyrazolines as antimicrobial agent. A. V. Dobaria and Co-workers[107] has discovered pyrazolines bearing chloroquinoline nucleus which used as antimicrobial agents(XIV).



(XIV) R = Aryl

Recently, Abd El-Galil E. Amr et. al.[108] have synthesised some new 3-substituted androstano[17,16-*c*]-52-aryl-pyrazolines and reported their antiandrogenic activity. Amir Azam and co-workers[109] have synthesised some pyrazoline derivatives and reported their antiamoebic activity.

Some of the compounds were found with IC50 lower than that of the standard drug metronidazole and thus are better inhibitor of growth of E. histolytica. Y. Rajendra Prasad et. al.[110] have synthesised some 1,3,5-triphenyl-2-pyrazolines and 3-(2''-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines and reported as antidepressant(XV) & (XVI).



(XV) R_1, R_2, R_3, R_4 = Alkyl (XVI)

Thus interesting biological activities of a novel heterocycles like pyrazolines have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system. In our search for new potential antimicrobial compounds, the reaction series of chalcones with hydrazine hydrate/phenylhydrazine under different conditions has been investigated and the pharmacological profile of the compounds have been studied and described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

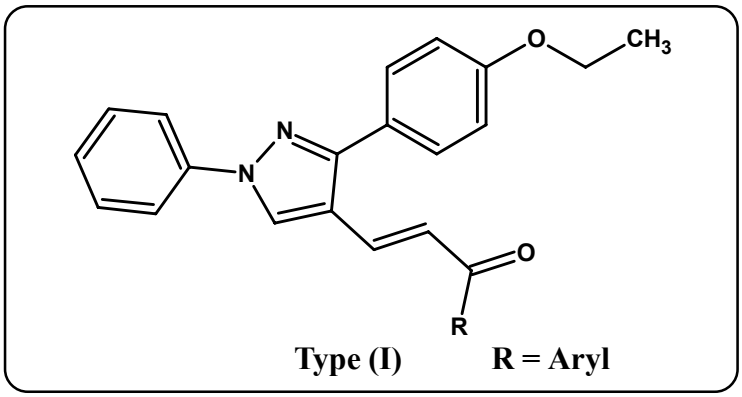
SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*- ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

SECTION-III : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXY- PHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

The chemistry of chalcones have generated intensive scientific studies throughout the world, specially interesting for their biological and industrial applications. With a view to obtaining compounds with better therapeutic activity, we have synthesized 1-aryl-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-ones by the condensation of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with various aromatic ketones in the presence of 40 % NaOH.



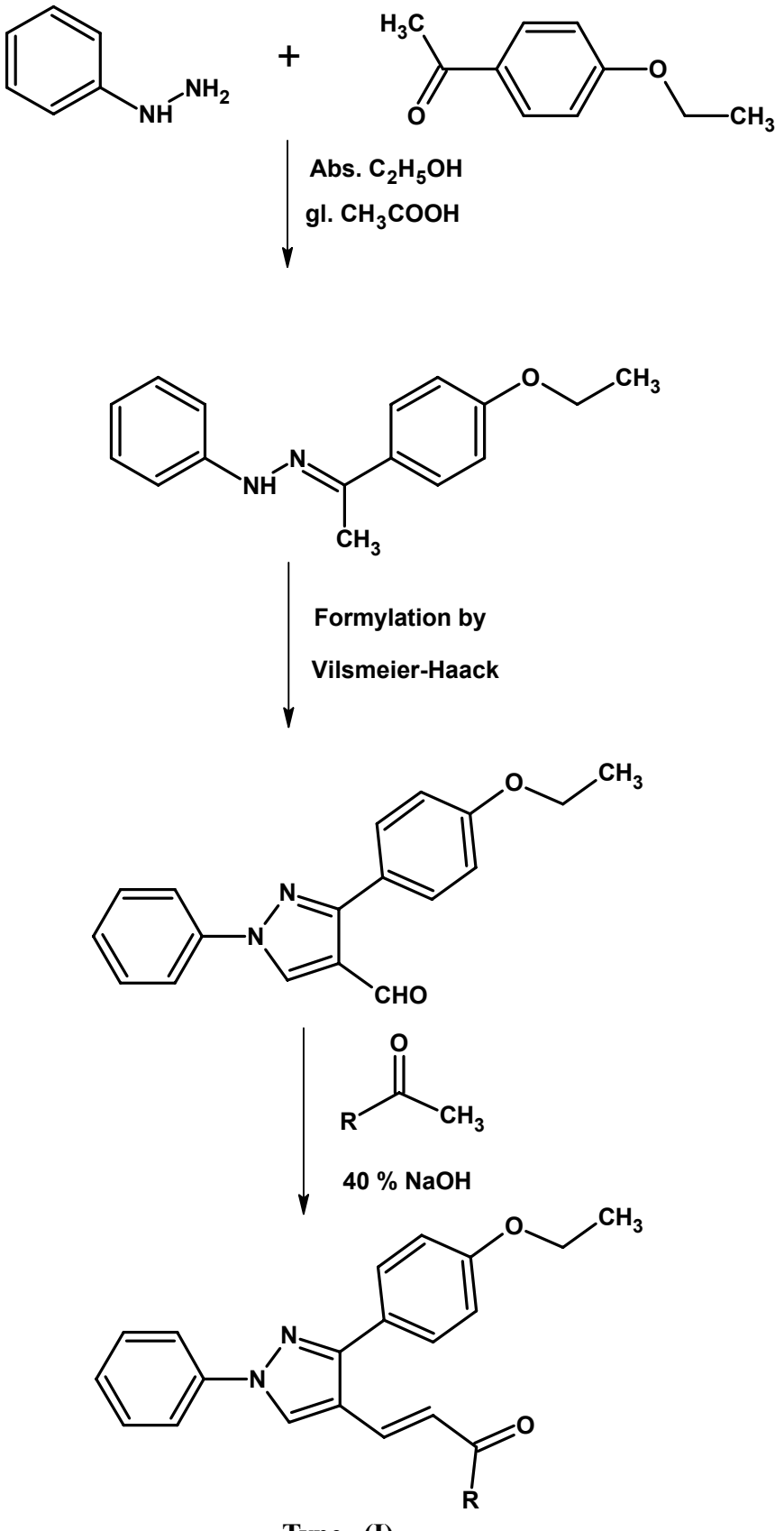
Type (I) **R = Aryl**

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis H37 Rv*** at concentration of 6.25 µg/ml using rifampin as standard drug.

REACTION SCHEME



Type - (I) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

A mixture of phenylhydrazine (1.08 g, 0.01 M) and *p*-ethoxyacetophenone (1.64 g, 0.01 M) in absolute ethanol was refluxed in water bath for 1 hrs. in the presence of 1ml glacial acetic acid. Product obtained after cooling was crystallised from absolute ethanol. Yield 92%, m.p. 63^{o}C ($C_{16}H_{18}N_2O$; Required : C, 75.56;H, 7.13, N, 11.01; Found : C, 75.51; H, 7.09; N,10.95%).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

p-Ethoxyphenylhydrazone(2.54 g, 0.01 M) was added into a Vilsmeier-Haack reagent (prepared by dropwise addition of 3 ml $POCl_3$ in ice cooled 25 ml DMF) and refluxed for 5 hrs. The reaction mixture was poured on to crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallised from methanol. Yield 80%, m.p. 120^{o}C ($C_{18}H_{16}N_2O_2$; Required : C, 73.95; H, 5.52; N, 9.58; Found : C, 73.89; H, 5.48; N, 9.52%).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

To a solution of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole (2.92 g, 0.01 M), and *p*-bromoacetophenone (1.99 g, 0.01 M) in ethanol (25 ml) , 40% NaOH added till the solution become basic. The reaction mixture was stirred for 24 hrs. The contents were poured on to crushed ice. Upon neutralization the solid was separated and crystallised from ethanol. Yield 65%, m.p.168^{o}C ($C_{26}H_{21}BrN_2O_2$; Required : C, 65.97; H, 4.47; N, 5.92; Found : C, 65.91; H, 4.41; N, 5.87%).

TLC solvent system : Acetone : Benzene (1.5 : 8.5).

Similarly other 1-aryl-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-ones have been prepared. The physical data are recorded in Table No. 1.

(D) Antimicrobial activity of 1-Aryl-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-ones

All the compounds have been evaluated for antimicrobial and antitubercular activity as described under.

(a) Antimicrobial activity

Antimicrobial activity was carried out by cup-plate agar diffusion method[418] which has been described as under.

(I) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B. coccus, S. aureus, E.aerogenes, P. aeruginosa*** in separate conical flasks at 40-50^{o}C and mixed well by gentle shaking. About 25ml content of the flask were poured and evenly spreaded in a petridish (13cm in diameter) and allowed to set for 2 hrs. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.

The plates were incubated at 37^{o}C for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded in Graphical Chart No.1.

The antibacterial activity data of the synthesised compounds have been compared with standard antibiotics like amoxicillin, benzoyl penicillin, ciprofloxacin and erythromycin.

(II) Antifungal activity

A. niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilized Sabouraud's agar medium was inoculated with 72 hrs. old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameter) were punched and filled with 0.04 ml (40 mg) solution of sample in DMF. The plates were incubated at 30^{o}C for 48

hrs. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled with solvent which act as control. The zones of inhibition were compared with standard antifungal greseofulvin. The zones of inhibition are recorded in Graphical Chart No. 1.

(b) Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and Co-ordination Facility (TAACF), U.S.A. Primary screening of the compounds for the antitubercular activity have been conducted at 6.25 mg/ml towards ***Mycobacterium tuberculosis H37Rv*** in BACTEC 12B using the BACTEC 460 radiometric system. The compounds demonstrating atleast>90% inhibition in the primary screening has been tested at lower concentration towards ***Mycobacterium tuberculosis H37Rv*** to determine the actual minimum inhibitory concentration (MIC) in the BACTEC-460.

The antitubercular activity data have been compared with standard drug rifampin at 0.25 mg/ml concentration and it showed 98% inhibition.

ANTIMICROBIAL ACTIVITY

Method	:	Cup-Plate[418]
Gram positive bacteria	:	***B. coccus***
		S. aureus
Gram negative bacteria	:	***E.aerogenes***
		P.aeruginosa
Fungi	:	***A. niger***
Concentration	:	40µg/ml
Solvent	:	Dimethyl formamide
Standard drugs	:	Amoxicillin, Benzoyl penicillin, Ciprofloxacin, Erythromycin Greseofulvin

The antimicrobial activity was compared with standard drugs viz amoxicillin, benzoyl penicillin, ciprofloxacin, erythromycin and antifungal activity was compared with viz greseofulvin. The inhibition zones were measured in mm.

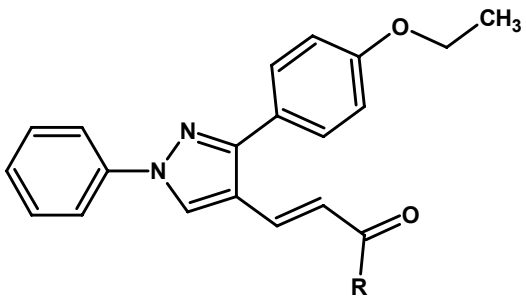
ANTITUBERCULAR ACTIVITY

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) U.S.A.

Method	:	BACTEC 460 Radiometric system.
Bacteria	:	***Mycobacterium Tuberculosis $H_{37}Rv$***
Concentration	:	6.25 µg/ml.
Standard drug	:	Rifampin.

The antitubercular activity data are showed in Table No. 1a.

TABLE NO. 1a : DATA OF *IN VITRO* EVALUATION OF ANTITUBERCULAR ACTIVITY



R = Aryl

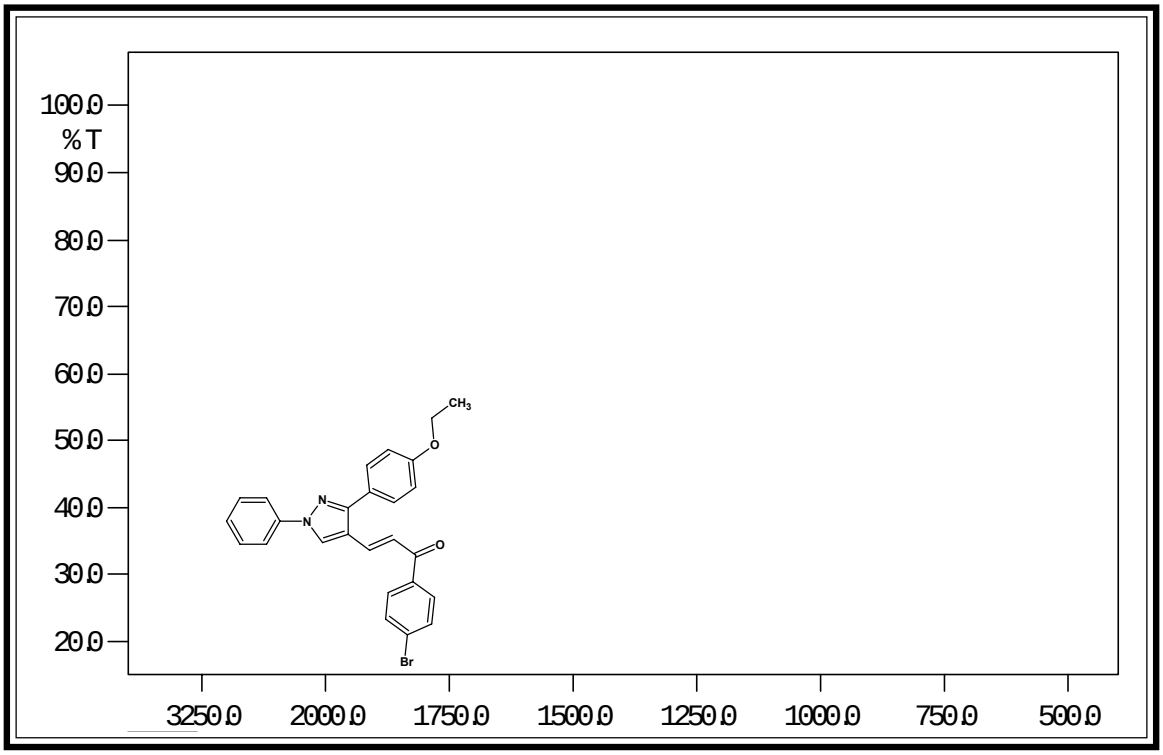
TAACF, Southern Research Institute Dr. H. H. Parekh

Primary Assay Summary Report Saurashtra University

Sample ID	Corp ID	Where,R= Strain	Supplier	Assay	MIb	MIC µg/ml	% Inhib	Activity
295669	NV-3	4-Br-C_6H_4-	Sau.uni	Alamar	H37Rv	>6.25	97	+
295658	NV-2	4-Cl-C_6H_4-	Sau. uni.	Alamar	H37Rv	>6.25	96	+
295673	NV-7	2-OH-C_6H_4-	Sau.uni	Alamar	H37Rv	>6.25	94	+
295678	NV-12	4-OCH_3-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	92	+
295670	NV-4	4-F-C_6H_4-	Sau.uni	Alamar	H37Rv	>6.25	61	-
295677	NV-11	4-CH_3-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	44	-
295667	NV-1	-C_6H_5	Sau.uni	Alamar	H37Rv	>6.25	38	-
295672	NV-6	3-NO_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	12	-
295675	NV-9	4-NO_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	06	-
295671	NV-5	2--C_4H_3S	Sau.uni	Alamar	H37Rv	>6.25	05	-
295676	NV-10	4-NH_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	02	-
295674	NV-8	4-OH-C_6H_4-	Sau.uni	Alama	H37Rv	>6.25	01	-

NIAID/ Southern Research institute/ GWL Hansen's Center/Colorado state university proprietary info

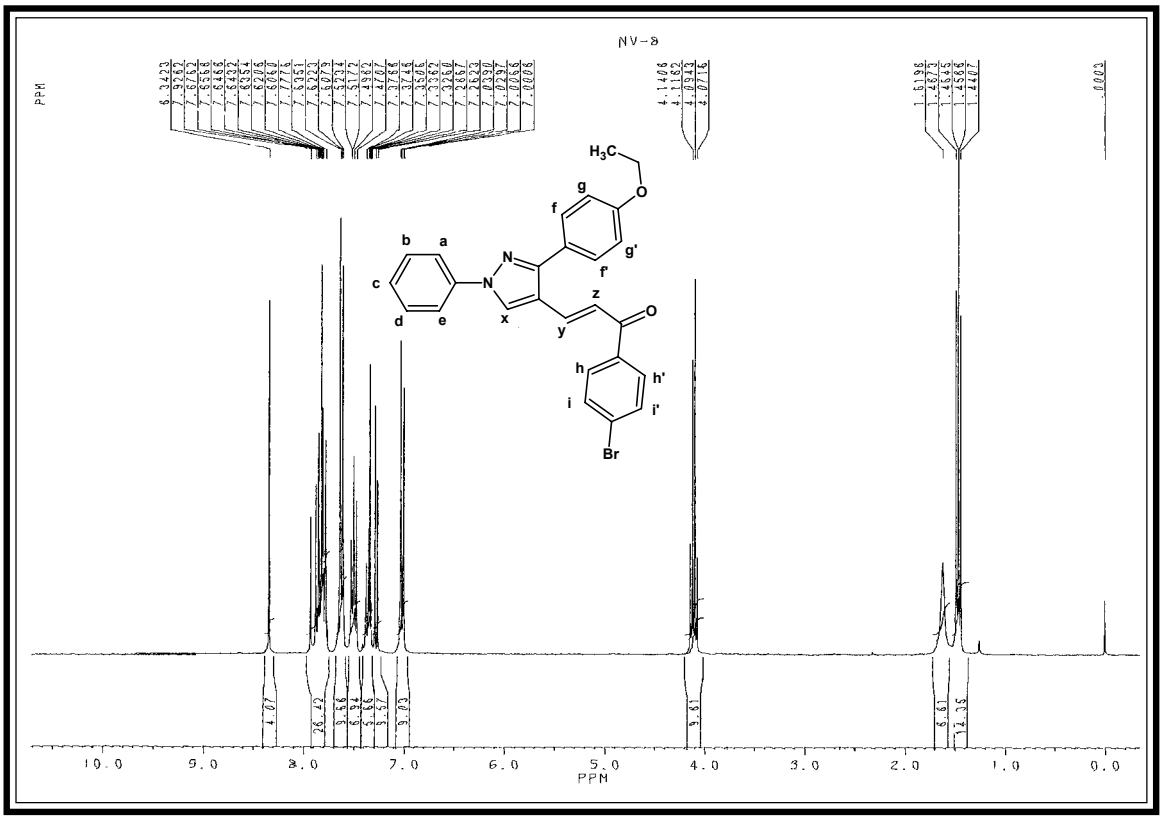
IR SPECTRAL STUDY OF 1-(*p*-BROMOPHENYL)-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2966	2975-2950	413
$-CH_3$	C-H str. (sym.)	2877	2880-2860	
	C-H i.p.def. (asym.)	1436	1470-1435	
	C-H o.o.p. def. (sym.)	1361	1390-1370	
Aromatic	C-H str.	3070	3080-3030	414
	C=C str.	1564	1585-1480	
	C-H i.p. def.	1093	1125-1090	
	C-H o.o.p. def	817	835-810	
Pyrazole moiety	C=N str.	1596 (overlapped)	1630-1590	415
	C-N str.	1215	1230-1020	
Ether	C-O-C str. (asym.)	1215 (overlapped)	1275-1200	413
	C-O-C str. (sym.)	1064	1075-1020	
Chalcone	C=O str.	1660	1685-1645	416
	CH=CH	3070 (overlapped)	3050-3000	
Halide	C-Br str.	754	600-800	413

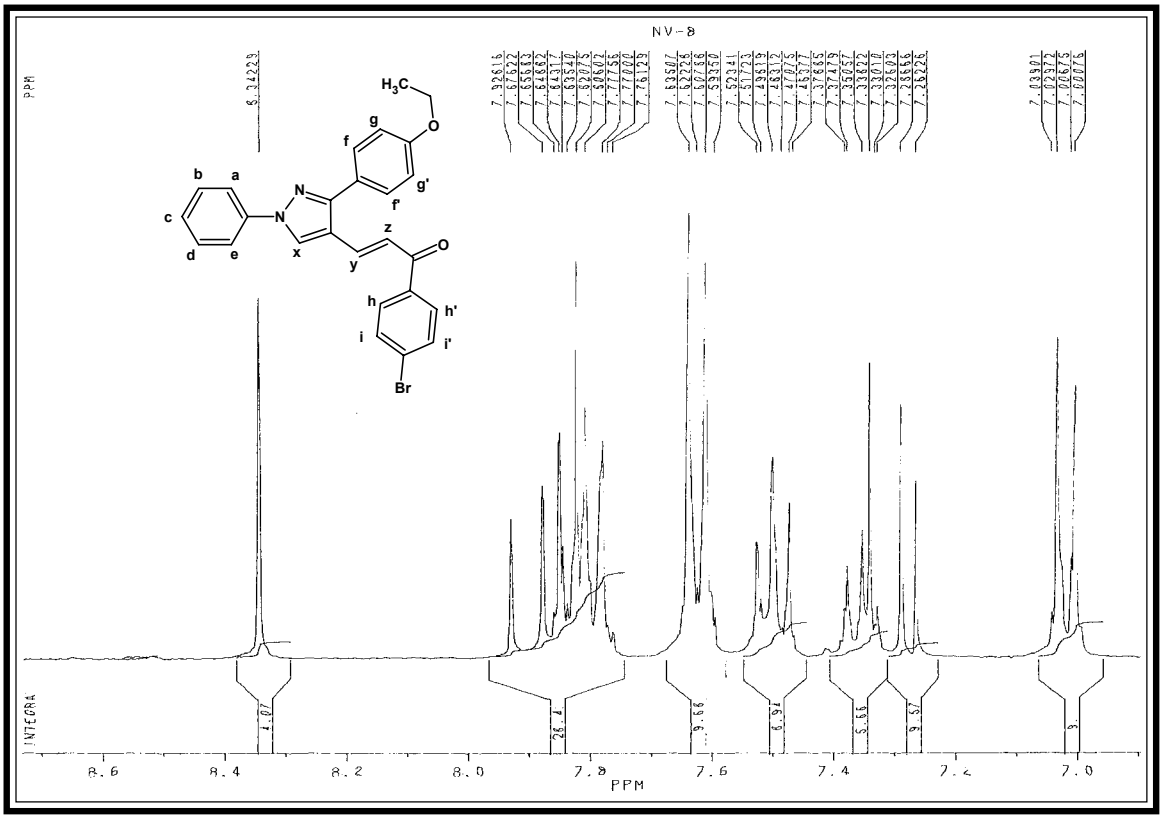
PMR SPECTRAL STUDY OF 1-(*p*-BROMOPHENYL)-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	RelativeNo. of Protons	Multiplicity	Inference	J Value In Hz
1.	1.44-1.46	3H	triplet	-$OCH_2\underline{CH_3}$	J_{CH_3}=7.1
2.	4.07-4.14	2H	quartret	-$O\underline{CH_2}CH_3$	J_{CH_2}=6.8
3.	7.00-7.02	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.7
4.	7.26-7.37	3H	multiplet	Ar-H_{ace}	-
5.	7.40-7.52	2H	triplet	Ar-H_{bd}	-
6.	7.59-7.62	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.4
7.	7.77-7.80	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.7
8.	7.80-7.85	1H	doublet	CH_z(vinylic)	J_{zy}=15
9.	7.82-7.84	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.4
10.	7.87-7.92	1H	doublet	$CHy_{(vinylic)}$	J_{yz}=15
11.	8.34	1H	singlet	CH_x	

EXPANDED AROMATIC REGION



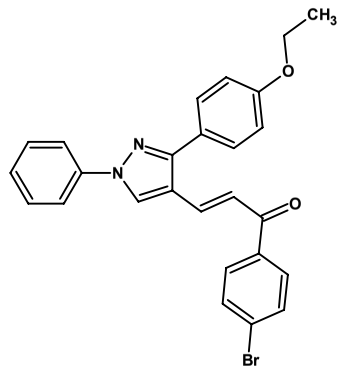
IR SPECTRAL STUDY OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Sr. No.	R	C=O str.
1a	C_6H_5-	1658
1b	4-NH_2-C_6H_4-	1660
1c	4-Cl-C_6H_4-	1658
1d	4-Br-C_6H_4-	1660
1e	4-F-C_6H_4-	1659
1f	2-OH-C_6H_4-	1657
1g	4-OH-C_6H_4-	1657
1h	4-OCH_3-C_6H_4-	1658
1i	4-CH_3-C_6H_4-	1656
1j	4-NO_2-C_6H_4-	1658
1k	3-NO_2-C_6H_4-	1659
1l	2-C_4H_3S-	1656

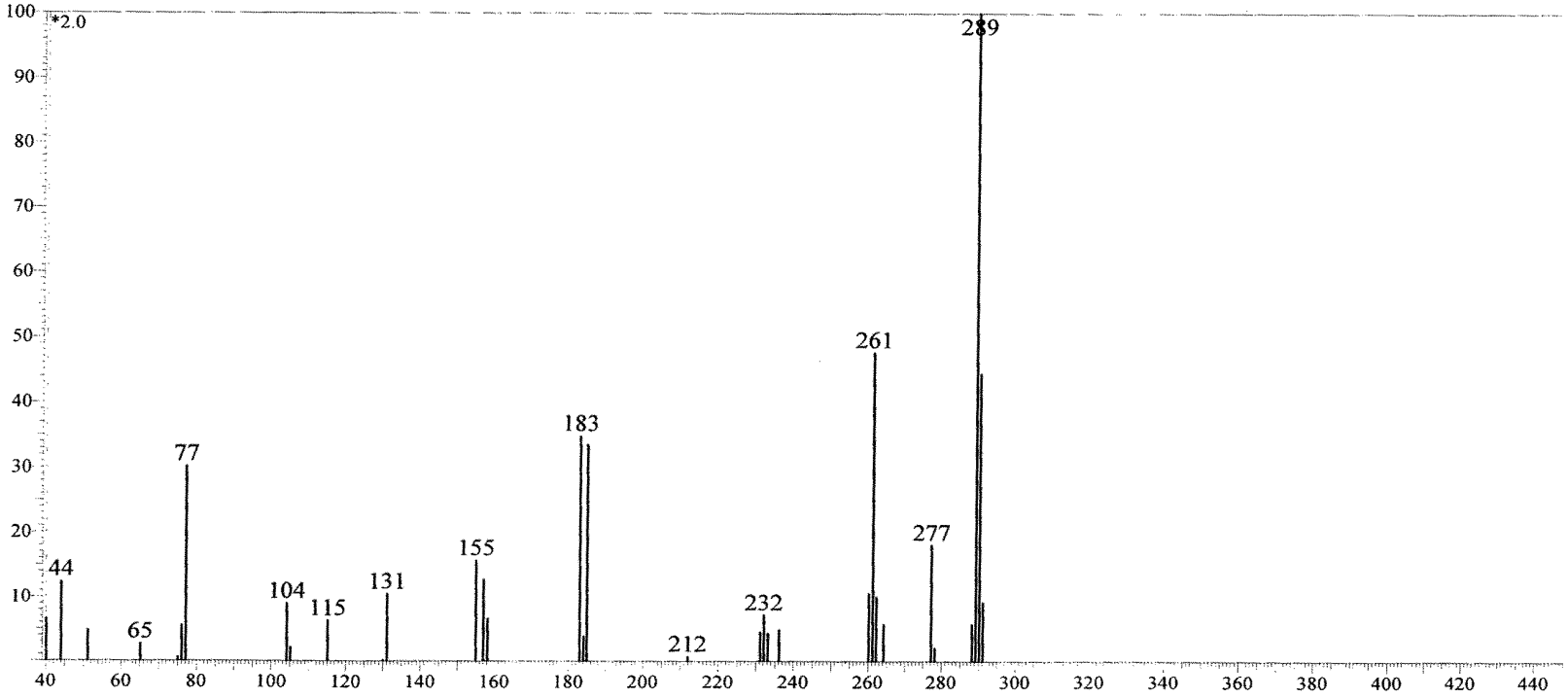
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information



Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 7/18/2005 11:27:49 AM
Sample Name : NV-11
Sample ID : NV-11
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-11.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune8.qgt

Line#:1 R.Time:7.8(Scan#:901)
MassPeaks:38 BasePeak:289(46014)
RawMode:Averaged 6.9-8.2(791-954)
BG Mode:None
intensity



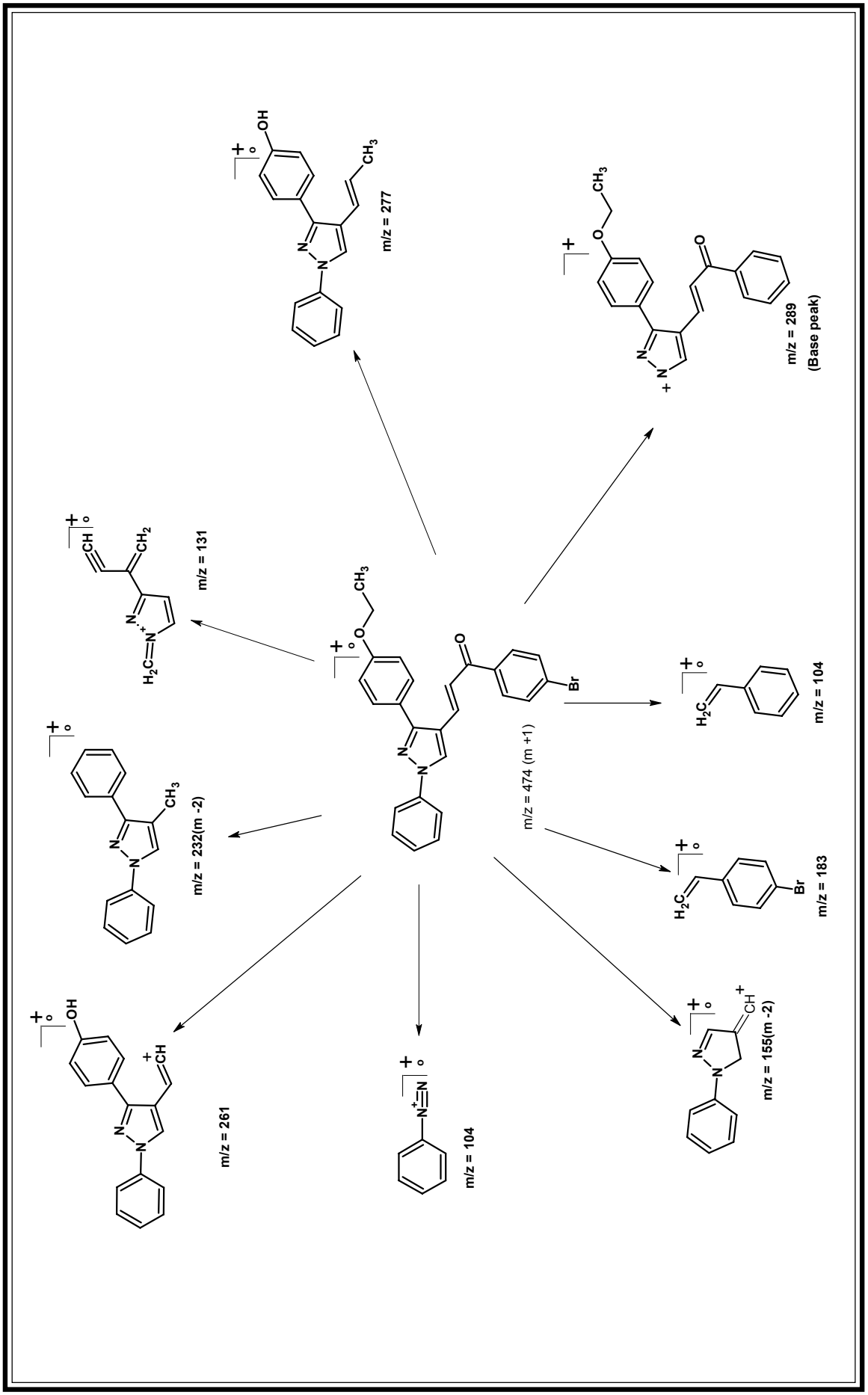
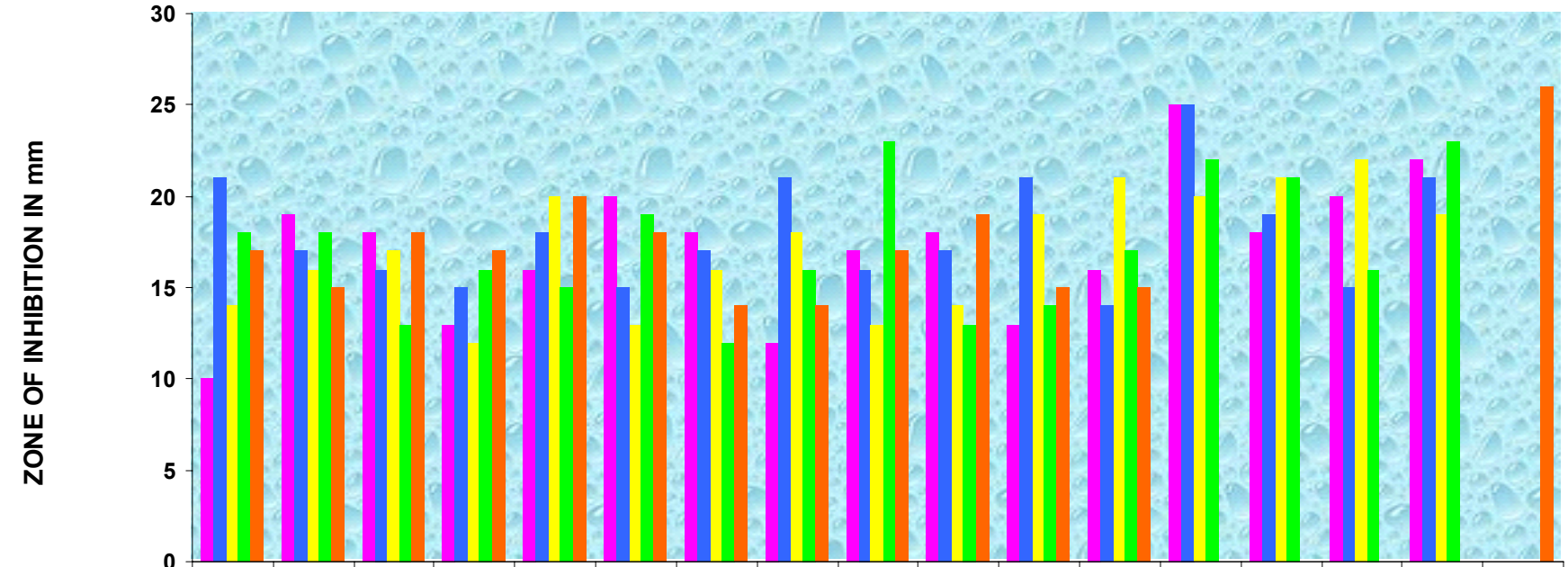

m/z = 474 (m +1)
m/z = 277
m/z = 289
(Base peak)
m/z = 131
m/z = 232(m -2)
m/z = 104
m/z = 183
m/z = 261
m/z = 104
m/z = 155(m -2)

TABLE-1 : PHYSICAL CONSTANTS OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES

Sr. No.	R Formula	Molecular Weight	Molecular ^{o}C	M. P Value	Rf* %	Yield Calcd.	% of Nitrogen Found	
1	2	3	4	5	6	7	8	9
1a	C_6H_5-	$C_{26}H_{22}N_2O_2$	394	124	0.54	62	7.10	7.05
1b	4-NH_2-C_6H_4-	$C_{26}H_{23}N_3O_2$	409	114	0.64	58	10.26	10.22
1c	4-Cl-C_6H_4-	$C_{26}H_{21}ClN_2O_2$	428.5	168	0.58	78	6.53	6.49
1d	4-Br-C_6H_4-	$C_{26}H_{21}BrN_2O_2$	473	168	0.42	65	5.92	5.87
1e	4-F-C_6H_4-	$C_{26}H_{21}FN_2O_2$	412	211	0.53	56	6.79	6.73
1f	2-OH-C_6H_4-	$C_{26}H_{22}N_2O_3$	410	124	0.68	67	6.82	6.78
1g	4-OH-C_6H_4-	$C_{26}H_{22}N_2O_3$	410	195	0.47	73	6.82	6.77
1h	4-OCH_3-C_6H_4-	$C_{27}H_{24}N_2O_3$	424	204	0.49	68	6.60	6.54
1i	4-CH_3-C_6H_4-	$C_{27}H_{24}N_2O_2$	408	145	0.71	58	6.86	6.81
1j	4-NO_2-C_6H_4-	$C_{26}H_{21}N_3O_4$	439	154	0.58	68	9.56	9.53
1k	3-NO_2-C_6H_4-	$C_{26}H_{21}N_3O_4$	439	173	0.65	69	9.56	9.54
1l	2-C_4H_3S-	$C_{24}H_{20}N_2O_2S$	400	146	0.49	52	6.99	6.95

*TLC Solvent System : Acetone : Benzene (1.5 : 8.5)

GRAPHICAL CHART NO. 1 : ANTIMICROBIAL ACTIVITY OF 1-ARYL-3-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-2-PROPEN-1-ONES



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxicillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	10	19	18	13	16	20	18	12	17	18	13	16	25	18	20	22	0
S. aureus	21	17	16	15	18	15	17	21	16	17	21	14	25	19	15	21	0
E. aerogenes	14	16	17	12	20	13	16	18	13	14	19	21	20	21	22	19	0
P. aeruginosa	18	18	13	16	15	19	12	16	23	13	14	17	22	21	16	23	0
A. niger	17	15	18	17	20	18	14	14	17	19	15	15	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of chalcones (type-I) revealed that all the compounds were able to inhibit the growth of Gram positive & Gram negative bacterial strains.

In case of Gram positive bacterial strain maximum activity was observed in compound bearing R = 2-hydoxyphenyl and 4-bromophenyl against ***B. coccus***. The significant activity was displayed by compound having R=Phenyl, 4-chlorophenyl,4-anisyl and 3-nitrophenyl against ***S. aureus***.

In case of Gram negative bacterial strain all the compounds were least active against ***Pseudomonas,*** except R= 4-hydroxyphenyl and 2-thiophene. The compounds having R=4-chlorophenyl and 4-anisyl have shown good activity against ***Aerogenes.***

ANTIFUNGAL ACTIVITY

All the compound exhibited mild activity against fungal strain ***A. niger*** except compounds having R= 4-aminophenyl and 4-hydaroxyphenyl which showed good activity against ***A. niger***.

The antimicrobial activity shown by compounds was compared with known antibiotics like amoxycillin, benzoylpenicillin, ciprofloxacin,erythromycin & greseofulvin.

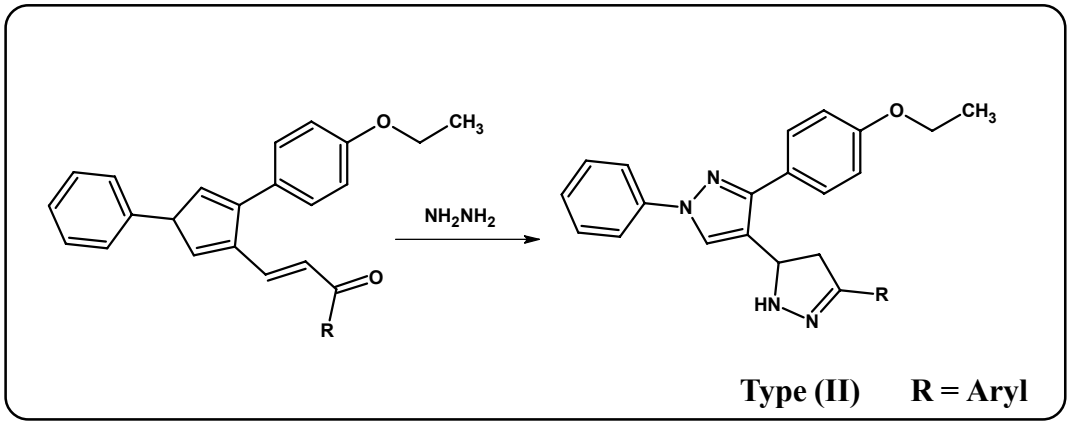
ANTITUBERCULAR ACTIVITY

The compounds having R = 4-bromophenyl,4-chlorophenyl,2-hydroxyphenyl and 4-anisyl have displayed percentage inhibition in the range of 98-90% and compounds bearing R = 4-fluorophenyl and 4-tolyl showed percentage inhibition in the range of 60-40% against ***Mycobacterium tuberculosis H37 Rv***.The antitubercular activity data have been compared with standard drug rifampin.

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

Pyrazoline derivatives represent one of the most active class of compounds having a wide spectrum of biological activities. Looking to the interesting properties of pyrazolines it was considered worthwhile to synthesise a series of pyrazolines of type-(II) for obtaining biologically potent agents which were prepared by reacting chalcones of type (I) with phenylhydrazine in the presence of piperidine.

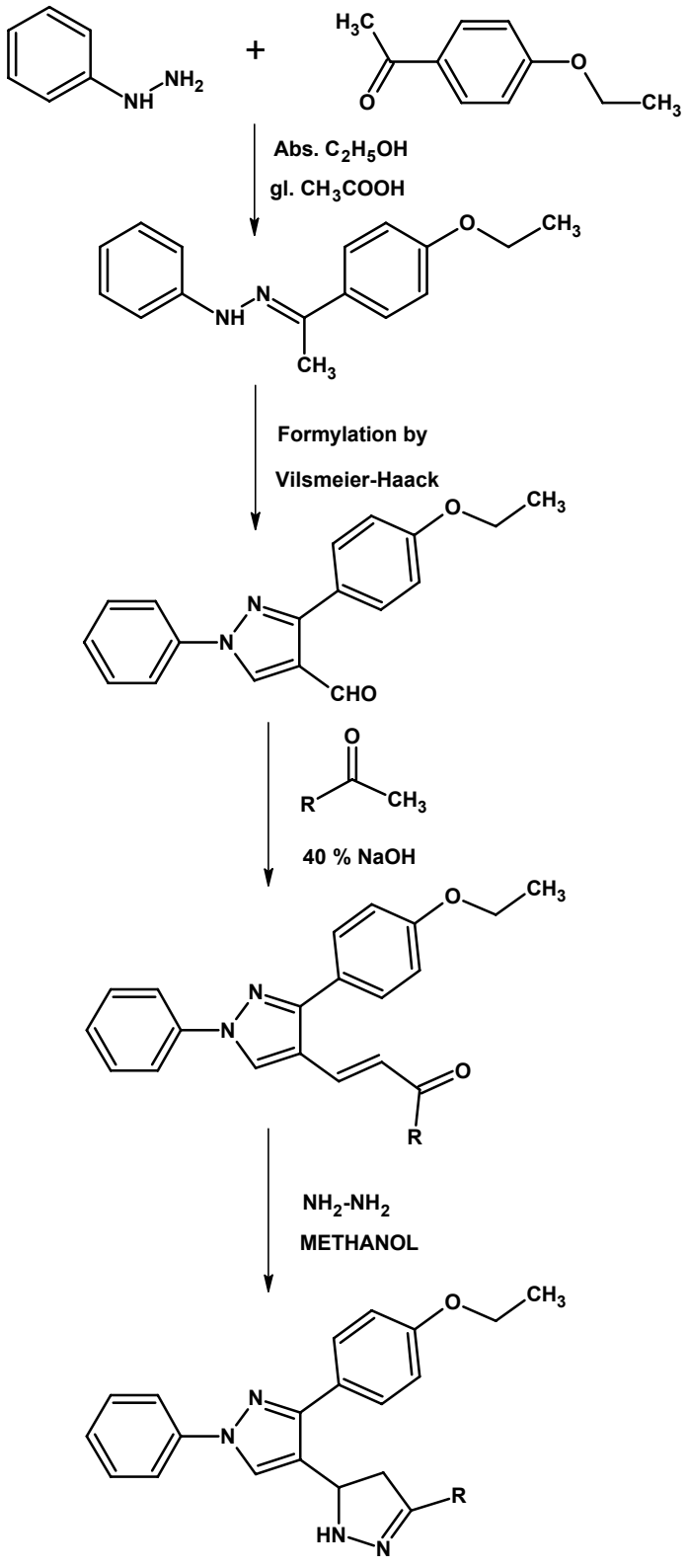


Type (II) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (II) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

See [A] Part-I, Section-I (C).

(D) Synthesis of 3-(*p*-Bromophenyl)-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazoline

A mixture of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.87 g, 0.01 M), hydrazine hydrate (1.08 g, 0.01 M) in 25 ml methanol was refluxed for 10 hrs. . The reaction mixture was poured on to crushed ice. The product was isolated and crystallised from ethanol. Yield 68%, m.p. 123^{O}C ($C_{26}H_{23}BrN_4O$; Required : C, 64.07; H, 4.76; N, 11.50; Found : C, 64.02; H, 4.69; N, 11.45%).

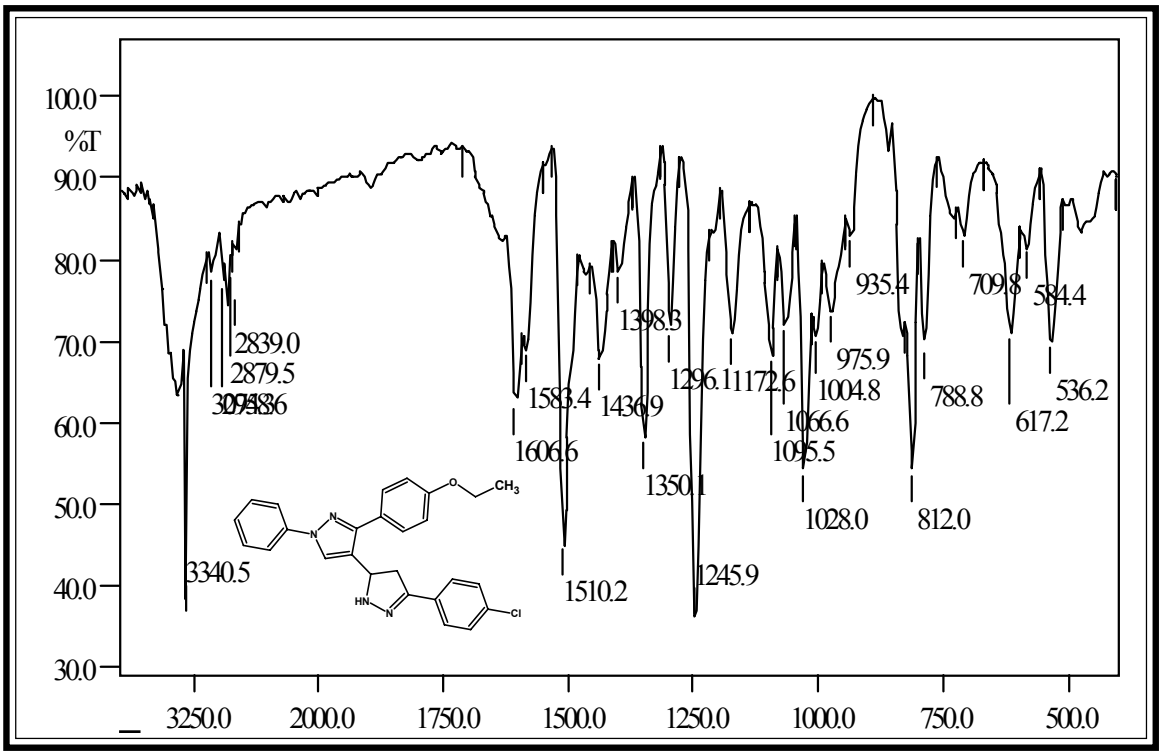
TLC solvent system : Acetone : Benzene (1 : 9).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 2.

(E) Antimicrobial activity of 3-Aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 2.

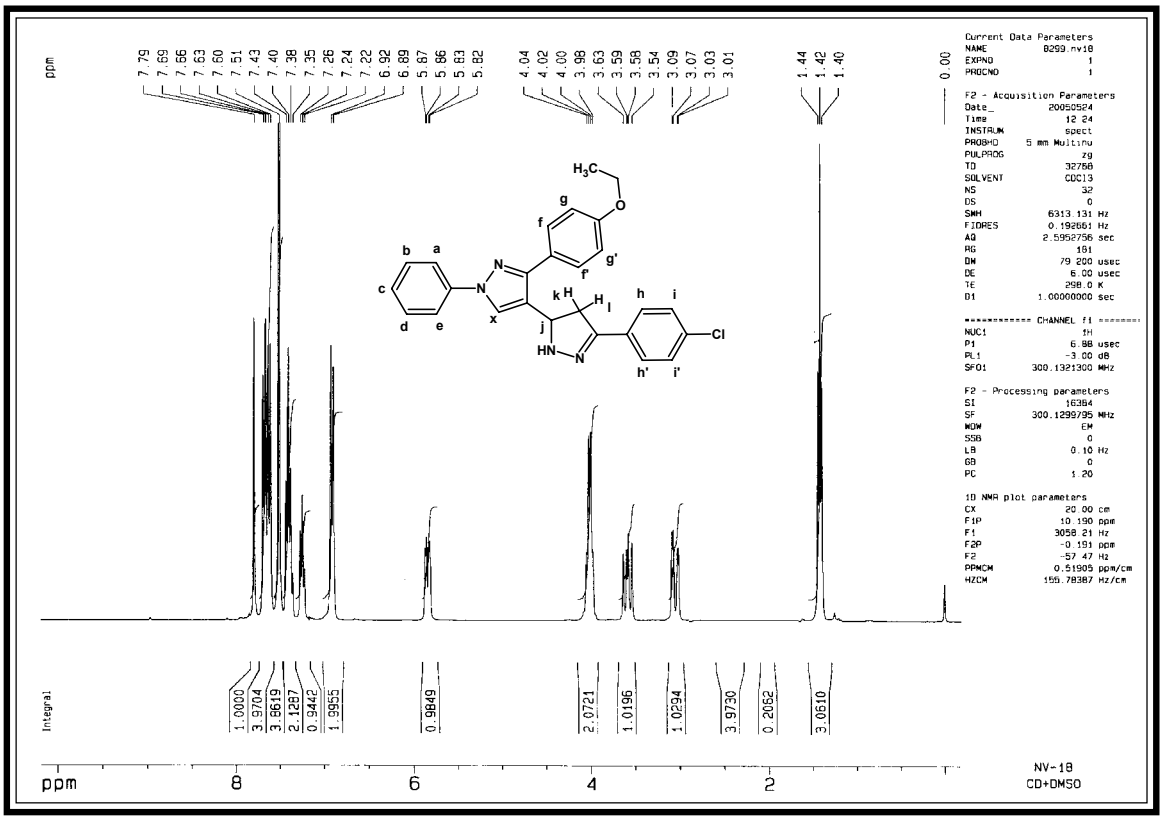
IR SPECTRAL STUDY OF 3-(*p*-TOLYL)-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2948	2975-2950	413
$-CH_3$	C-H str. (sym.)	2879	2880-2860	
	C-H i.p.def. (asym.)	1436	1470-1435	
	C-H o.o.p. def. (sym.)	1398	1390-1370	
Aromatic	C-H str.	3074	3080-3030	414
	C=C str.	1583	1585-1480	
	C-H i.p. def.	1095	1125-1090	
	C-H o.o.p. def	812	835-810	
Pyrazole	C=N str.	1606	1630-1590	415
moiety	C-N str.	1066	1230-1020	
Ether	C-O-C str. (asym.)	1245	1275-1200	413
	C-O-C str. (sym.)	1028	1075-1030	
Pyrazoline	C=N str.	1583 (overlapped)	1630-1590	417
	C-N str.	1172	1230-1020	
Halide	C-Br str.	788	600-800	413

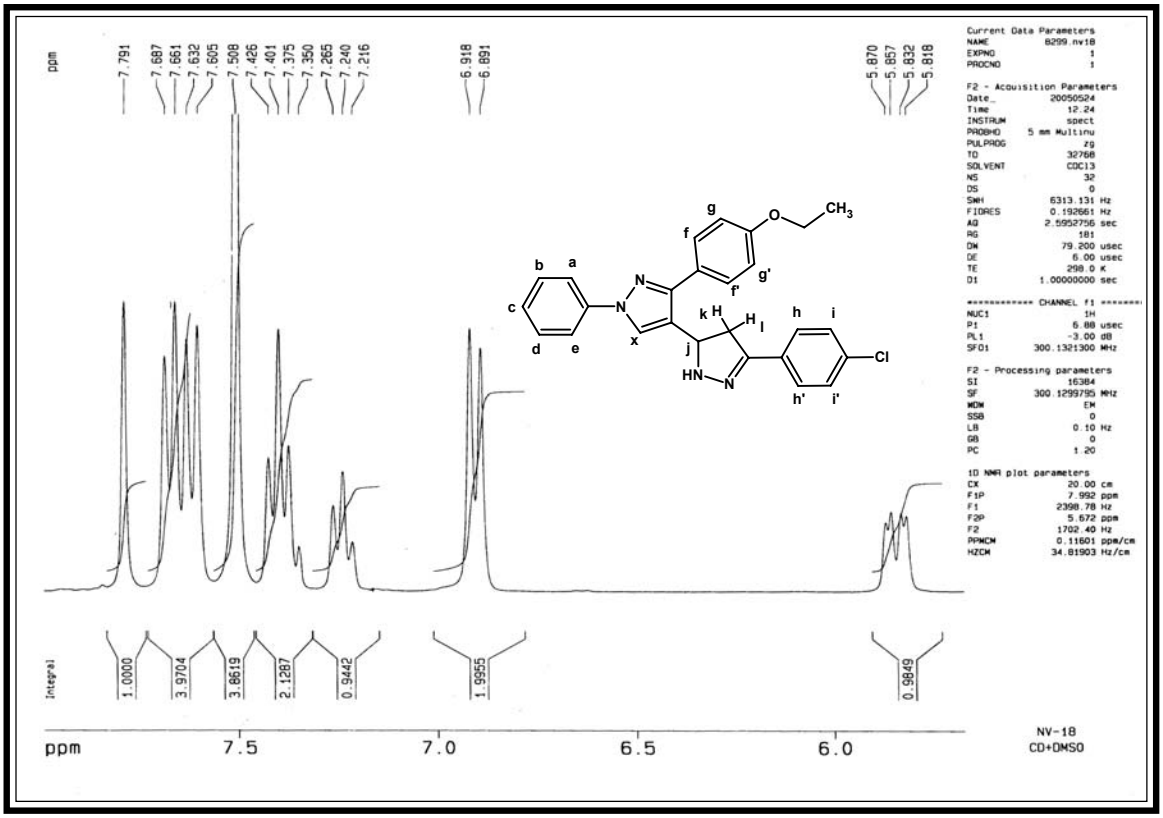
PMR SPECTRAL STUDY OF 3-(*p*-CHLOROPHENYL)-5-(1',N- PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE

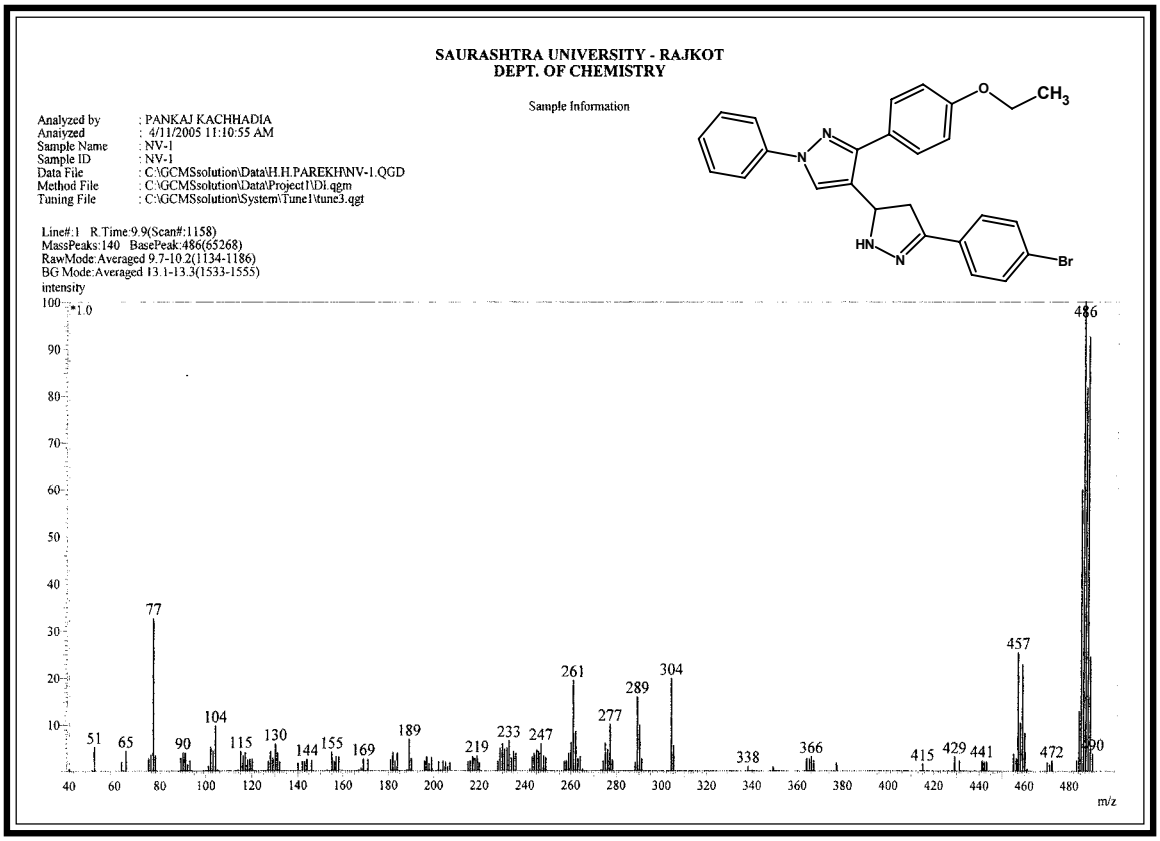


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	RelativeNo. of Protons	Multiplicity	Inference	J Value In Hz
1.	1.40-1.44	3H	triplet	$-OCH_2\underline{C}H_3$	$JCH_3 = 6.0$
2.	3.01-3.09	1H	double	CH_l	$J_{lk} = 15$
			doublet		$J_{ij} = 6.0$
3.	3.54-3.63	1H	double	CH_k	$J_{kl} = 15$
			doublet		$J_{kj} = 3.0$
4.	3.98-4.04	2H	quartret	$-OC\underline{H}_2CH_3$	$JCH_2 = 6.0$
5.	5.82-5.87	1H	double	CH_j	$J_{jk} = 12.0$
			doublet		$J_{ji} = 3.0$
6.	6.89-6.91	2H	doublet	Ar-$H_{ff'}$	$J_{fg} = 8.1$
7.	7.21-7.26	1H	triplet	Ar-H_c	-
8.	7.37-7.40	2H	triplet	Ar-H_{bd}	-
9.	7.50	4H	multiplat	Ar-H_{ae}Ar-$H_{ii'}$	-
10.	7.60-7.63	2H	doublet	Ar$H_{gg'}$	$J_{gh} = 8.1$
11.	7.66-7.68	2H	doublet	Ar$H_{hh'}$	$J_{hi} = 7.8$
12.	7.79	1H	singlet	CH_x	

EXPANDED AROMATIC REGION





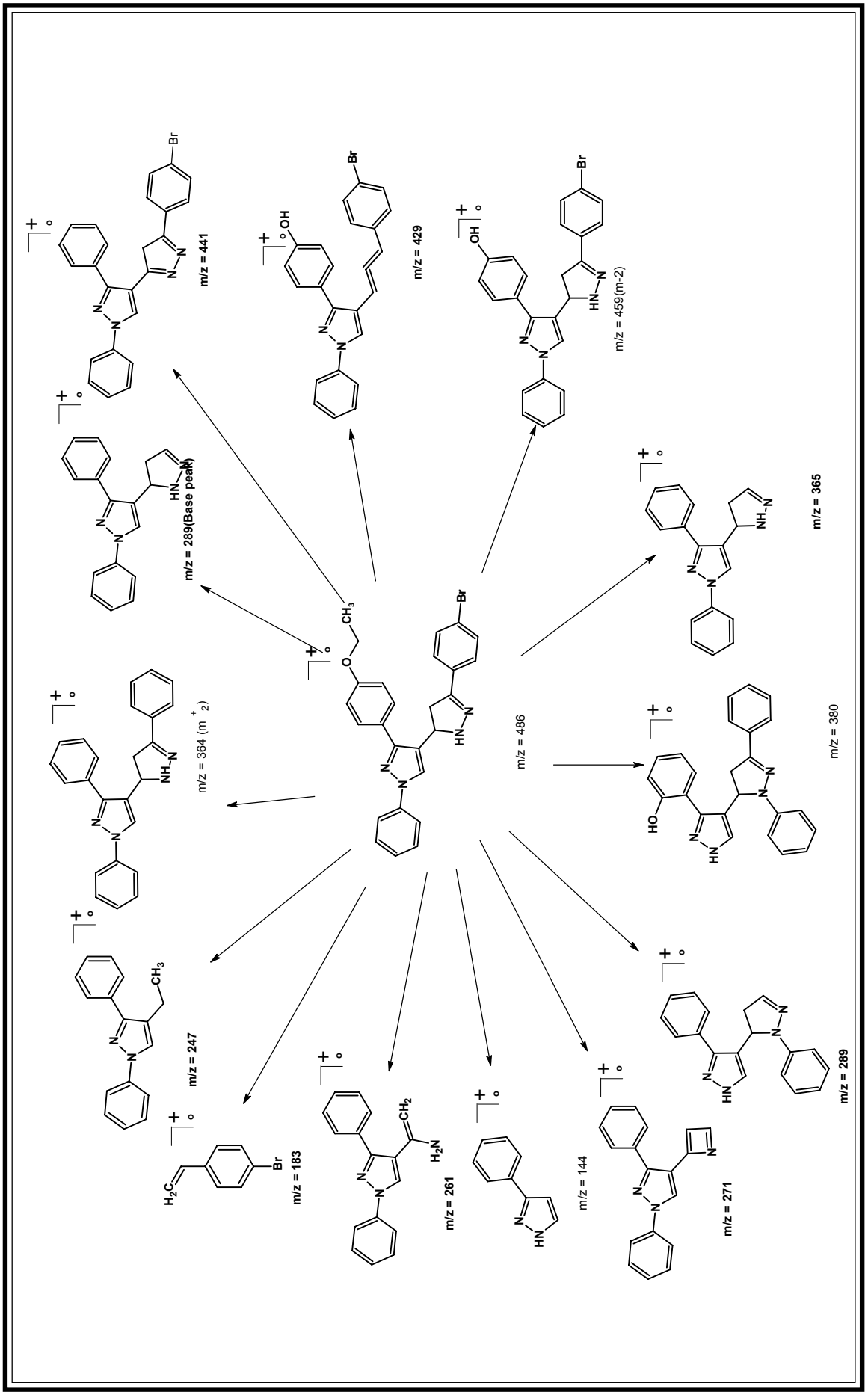
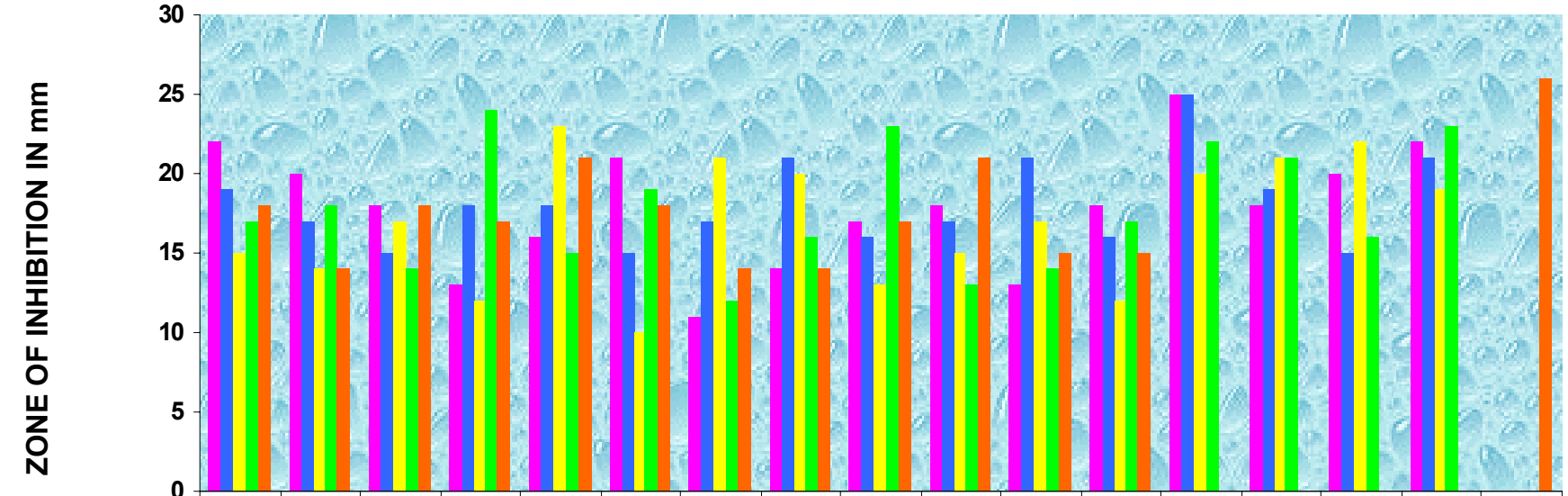

m/z = 486
m/z = 441
m/z = 429
m/z = 459(m-2)
m/z = 365
m/z = 380
m/z = 289(Base peak)
m/z = 364 (m+2)
m/z = 247
m/z = 183
m/z = 261
m/z = 144
m/z = 271
m/z = 289

TABLE-2 : PHYSICAL CONSTANTS OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL PYRAZOL-4'-YL) PYRAZOLINES

Sr. No.	R Formula	Molecular Weight	Molecular ^{o}C	M. P Value	Rf* %	Yield Calcd.	% of Nitrogen Found	
1	2	3	4	5	6	7	8	9
2a	C_6H_5-	$C_{26}H_{24}N_4O$	408	158	0.58	58	13.72	13.70
2b	4-NH_2-C_6H_4-	$C_{26}H_{25}N_5O$	423	110	0.55	58	16.54	16.49
2c	4-Cl-C_6H_4-	$C_{26}H_{23}ClN_4O$	442.5	101	0.61	58	12.65	12.60
2d	4-Br-C_6H_4-	$C_{26}H_{23}BrN_4O$	487	123	0.56	68	11.50	11.45
2e	4-F-C_6H_4-	$C_{26}H_{23}FN_4O$	426	170	0.67	64	13.14	13.08
2f	2-OH-C_6H_4-	$C_{26}H_{24}N_4O_2$	424	189	0.48	74	13.20	13.14
2g	4-OH-C_6H_4-	$C_{26}H_{24}N_4O_2$	424	175	0.53	64	13.20	13.15
2h	4-OCH_3-C_6H_4-	$C_{27}H_{26}N_4O_2$	438	132	0.58	62	12.78	12.73
2i	4-CH_3-C_6H_4-	$C_{27}H_{26}N_4O$	422	97	0.55	56	13.26	13.20
2j	3-NO_2-C_6H_4-	$C_{26}H_{23}N_5O_3$	453	146	0.64	64	15.44	15.40
2k	4-NO_2-C_6H_4-	$C_{26}H_{23}N_5O_3$	453	126	0.54	58	15.44	15.40
2l	2-C_4H_3S-	$C_{24}H_{22}N_4OS$	414	154	0.54	64	13.52	13.48

*TLC Solvent System : Acetone : Benzene (1 :9)

GRAPHICAL CHART NO. 2 : ANTIMICROBIAL ACTIVITY OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL4'-YL)PYRAZOLINES



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxicillin	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	22	20	18	13	16	21	11	14	17	18	13	18	25	18	20	22	0
S. aureus	19	17	15	18	18	15	17	21	16	17	21	16	25	19	15	21	0
E. aerogenes	15	14	17	12	23	10	21	20	13	15	17	12	20	21	22	19	0
P. aeruginosa	17	18	14	24	15	19	12	16	23	13	14	17	22	21	16	23	0
A. niger	18	14	18	17	21	18	14	14	17	21	15	15	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been observed from the experimental data that all compounds of type (II) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

However, the maximum activity was observed in compounds bearing R=phenyl and 2-hydroxyphenyl substituents against ***B.coccus***. The significant activity was observed in compounds bearing R=4-anisyl and 4-nitrophenyl against ***S.aureus.***

The maximum activity was displayed by the compounds bearing R=4-fluorophenyl against ***E.aerogenes***. In case of ***P.aeruginosa*** all the compounds were least active except R=4-bromophenyl and 4-tolyl.

ANTIFUNGAL ACTIVITY

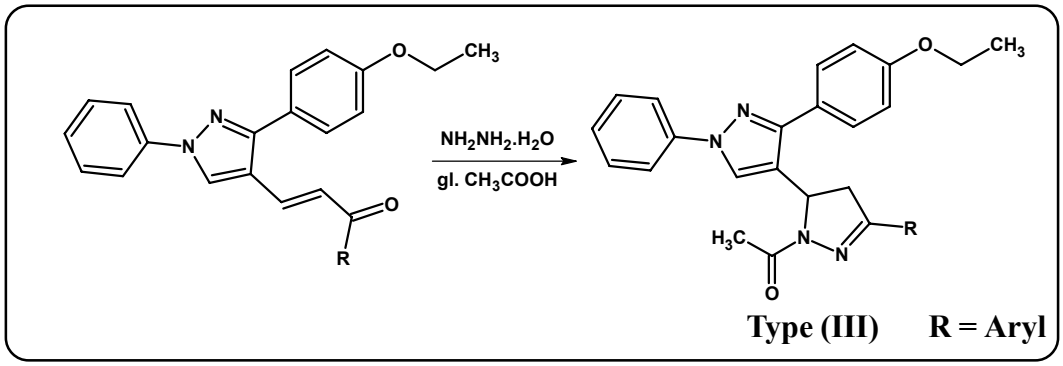
The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R=fluorophenyl and 3-nitrophenyl against ***A.niger***.

The antibacterial activity was compared with standard drug viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

SECTION - III

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

Pyrazoline derivatives represent one of the modest class of compounds possessing wide range of pharmacological activities.It was considered worthwhile to synthesise some new pyrazolines bearing 1,N-phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole nucleus. The preparation of 1,N-acetyl-3-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines (III) have been under taken by cyclocondensation of chalcones of type (I) with hydrazine hydrate in glacial acetic acid.



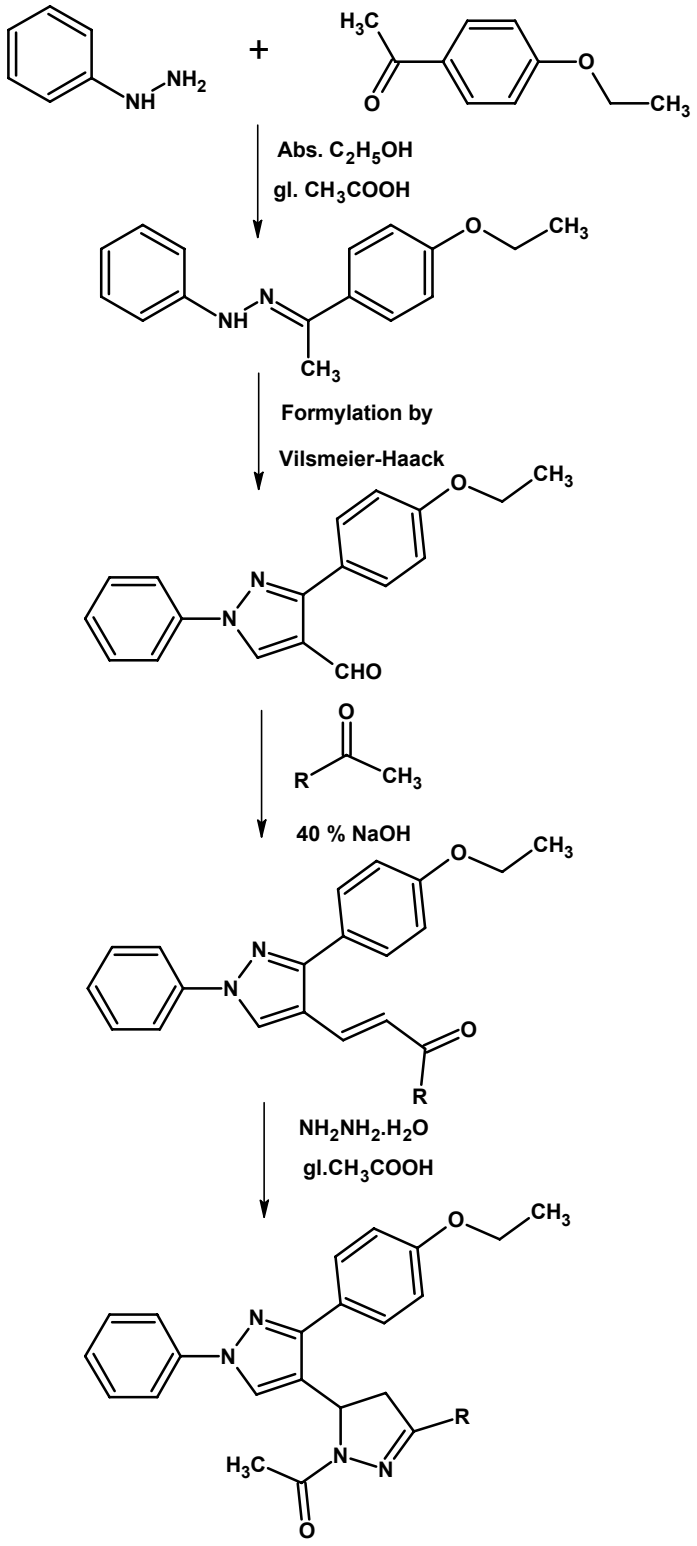
Type (III) **R = Aryl**

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of **Mycobacterium tuberculosisH37 Rv** at concentration of 6.25 µg/ml using rifampin as standard drug.

REACTION SCHEME



Type - (III) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

See [A] Part-I, Section-I (C).

(D) Synthesis of 1,N-Acetyl-3-(*p*-bromophenyl)-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazoline

A mixture of 1-(*p*-bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.73 g, 0.01 M) in 25 ml absolute alcohol, hydrazine hydrate (1 g, 0.02 M) and glacial acetic acid (10 ml) was refluxed for 8 hrs. The reaction mixture was poured on to crushed ice. The product was isolated and crystallised from ethanol. Yield 72%, m.p.93^{o}C ($C_{28}H_{25}BrN_4O_2$; Required : C, 63.52; H, 4.76; N, 10.58; Found : C, 63.46; H, 4.71; N, 10.54%).

TLC solvent system : Acetone : Benzene (1 : 9).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 3.

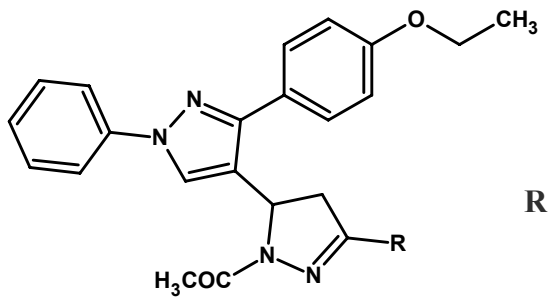
(E) Antimicrobial activity of 1,N-Acetyl-3-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 3.

(F) Anttubercular activity of 1,N-Acetyl-3-aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-pyrazolines

The antitubercular evaluation of the compounds was carried out as described in [A] Part-I, section-I (D). The antitubercular activity data are showen in Table No. 3a.

TABLE NO. 3a : DATA OF *IN VITRO* EVALUATION OF ANTITUBERCULAR ACTIVITY



R = Aryl

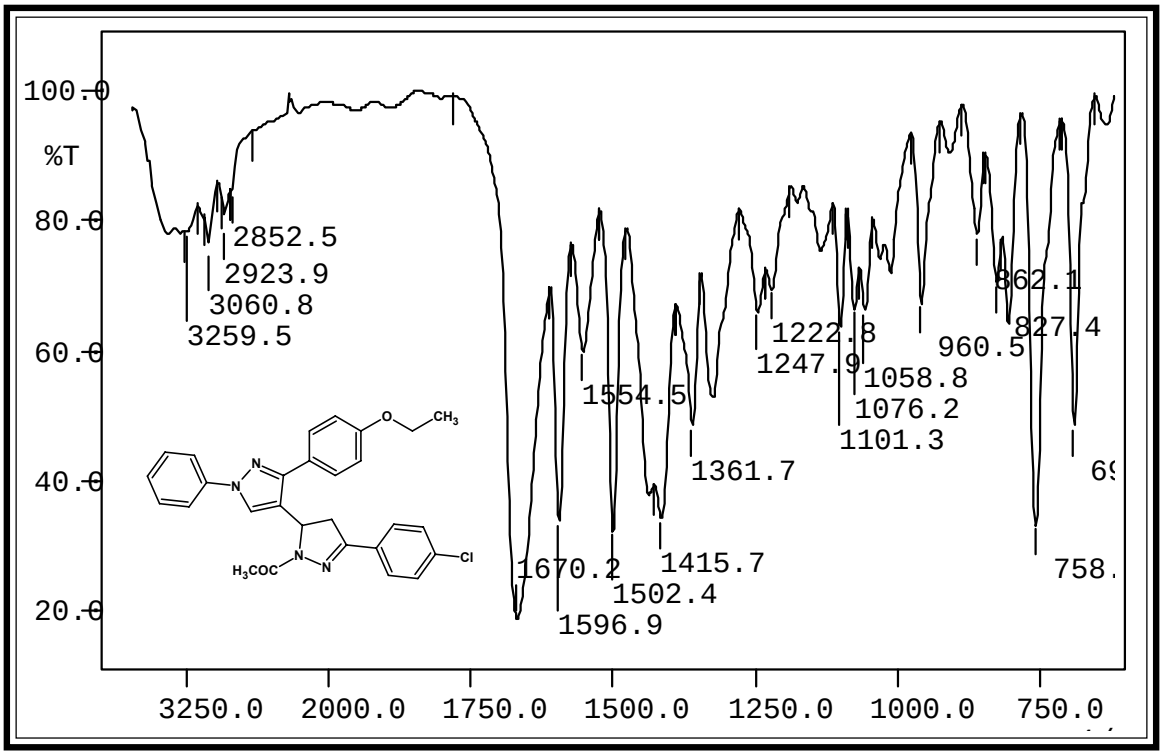
TAACF, Southern Research Institute Dr. H. H. Parekh

Primary Assay Summary Report Saurashtra University

Sample ID	Corp ID	Where,R= Strain	Supplier	Assay	MIb	MIC µg/ml	% Inhib	Activity
295684	NV-18	4-NO_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	80	-
295689	NV-23	4-CH_3-C_6H_4	Sau. uni	Alamar	H37Rv	>6.25	37	-
295680	NV-14	2-C_4H_3S-	Sau.uni	Alamar	H37Rv	>6.25	22	-
295681	NV-15	4-Br-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	15	-
295679	NV-13	-C_6H_5	Sau.uni	Alamar	H37Rv	>6.25	09	-
295685	NV-19	2-OH-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	09	-
295686	NV-20	4-OH-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	06	-
295687	NV-21	3-NO_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	04	-
295682	NV-16	4-F-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	00	-
295683	NV-17	4-NO_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.2	00	-
295688	NV-22	4-NH_2-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	00	-
295690	NV-24	4-OCH_3-C_6H_4	Sau.uni	Alamar	H37Rv	>6.25	00	-

NIAID/ Southern Research institute/ GWL Hansen's Center/Colorado state university proprietary info

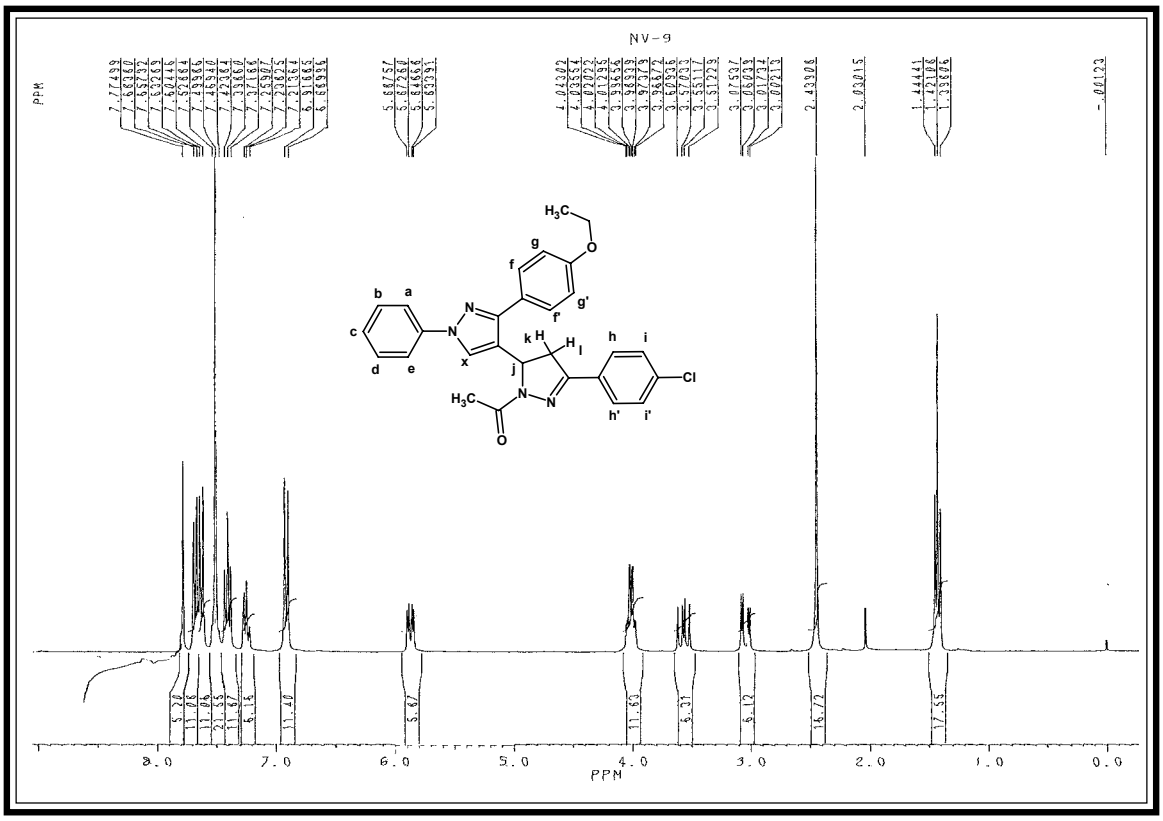
IR SPECTRAL STUDY OF 1,N-ACETYL-3-(*p*-CHLOROPHENYL)-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	413
$-CH_3$	C-H str. (sym.)	2852	2880-2860	
	C-H i.p.def. (asym.)	1415	1480-1435	
	C-H o.o.p. def. (sym.)	1361	1390-1370	
Aromatic	C-H str.	3060	3080-3030	414
	C=C str.	1554	1585-1480	
	C-H i.p. def.	1101	1125-1090	
	C-H o.o.p. def	827	835-810	
Pyrazole	C=N str.	1596	1630-1590	415
moiety	C-N str.	1101 (overlapped)	1230-1020	
Ether	C-O-C str. (asym.)	1247	1275-1200	413
	C-O-C str. (sym.)	1058	1075-1020	
Pyrazoline	C=O str.	1670	1660-1600	417
	C=N str.	1596	1630-1590	
	C-N str.	1247	1230-1020	
Halide	C-Cl str.	758	600-800	413

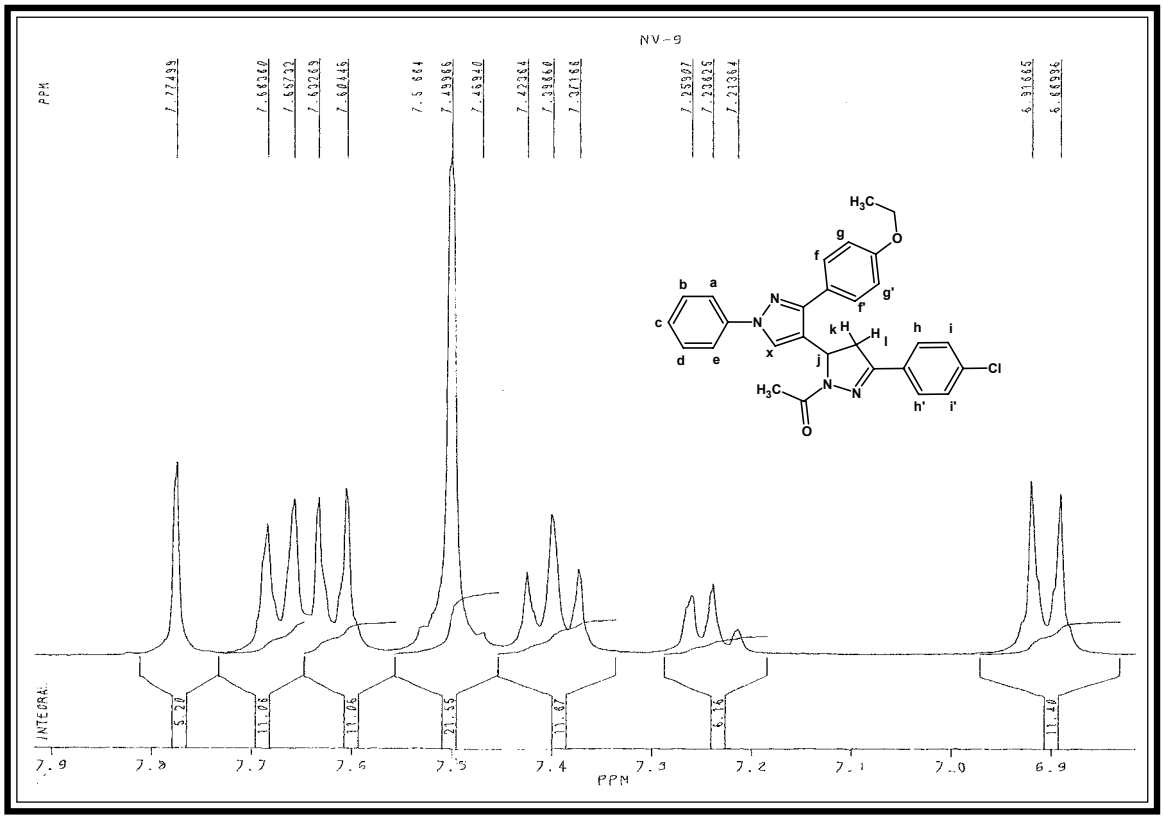
PMR SPECTRAL STUDY OF 1,N-ACETYL-3-(*p*-BROMOPHENYL)-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (400 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.39-1.44	3H	triplet	-$OCH_2\underline{CH_3}$	$J_{CH_3} = 6.9$
2.	2.43	3H	singlet	-$COCH_3$	-
3.	3.00-3.07	1H	double doublet	CH_l	$J_{lk} = 17.4$, $J_{lj} = 4.5$
4.	3.60-3.15	1H	double doublet	CH_k	$J_{kl} = 17.4$ $J_{kj} = 11.7$
5.	4.04-3.96	2H	quartret	-$\underline{OCH_2}CH_3$	$J_{CH_2} = 7.0$
6.	5.88-5.83	1H	double doublet	CH_j	$J_{jk} = 11.6$ $J_{jl} = 4.4$
7.	6.91-6.88	1H	doublet	Ar-$H_{ff'}$	$J_{fg} = 8.4$
8.	7.25-7.21	1H	triplet	Ar-H_c	-
9.	7.42-7.37	2H	triplet	Ar-H_{bd}	-
10.	7.63-7.60	2H	doublet	Ar-$H_{gg'}$	$J_{gf} = 8.4$
11.	7.49-7.46	4H	mulitplat	Ar-H_{ae},Ar-$H_{hh'}$	
12.	7.68-7.65	2H	doublet	Ar-$H_{ii'}$	$J_{ij} = 8.0$
13.	7.77	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION



IR SPECTRAL STUDY OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)PYRAZOLINES

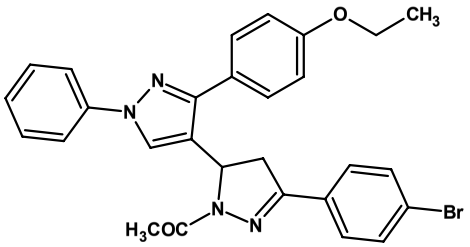
Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Sr. No.	R	C=O str.
4a	C_6H_5-	1666
4b	4-NH_2-C_6H_4-	1667
4c	4-Cl-C_6H_4-	1670
4d	4-Br-C_6H_4-	1668
4e	4-F-C_6H_4-	1669
4f	2-OH-C_6H_4-	1666
4g	4-OH-C_6H_4-	1668
4h	4-OCH_3-C_6H_4-	1669
4i	4-CH_3-C_6H_4-	1670
4j	4-NO_2-C_6H_4-	1668
4k	3-NO_2-C_6H_4-	1669
4l	2-C_4H_3S-	1665

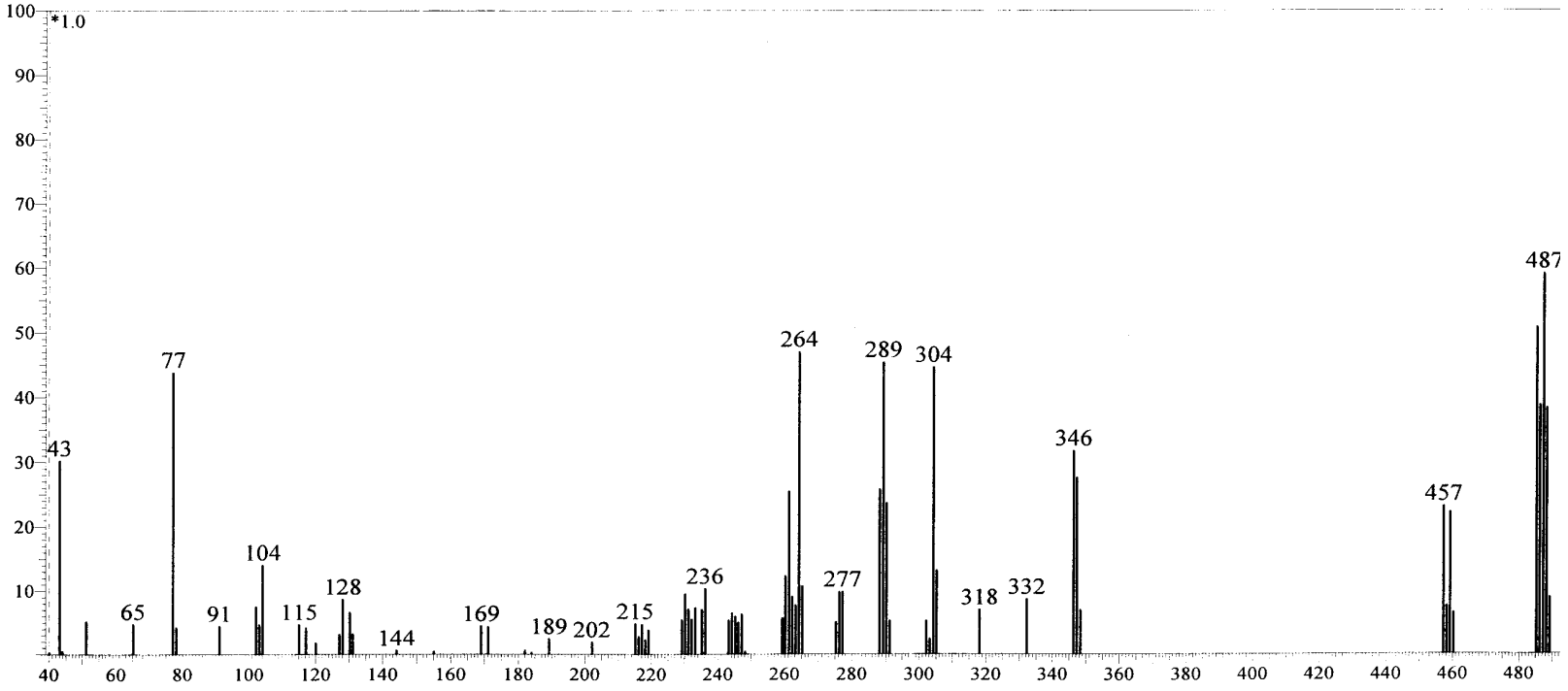
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 4/11/2005 12:34:39 PM
Sample Name : NV-3
Sample ID : NV-3
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-3.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt



Line#:1 R.Time:9.2(Scan#:1073)
MassPeaks:82 BasePeak:530(27214)
RawMode:Averaged 9.1-9.3(1062-1084)
BG Mode:Averaged 12.1-12.5(1421-1461)
intensity



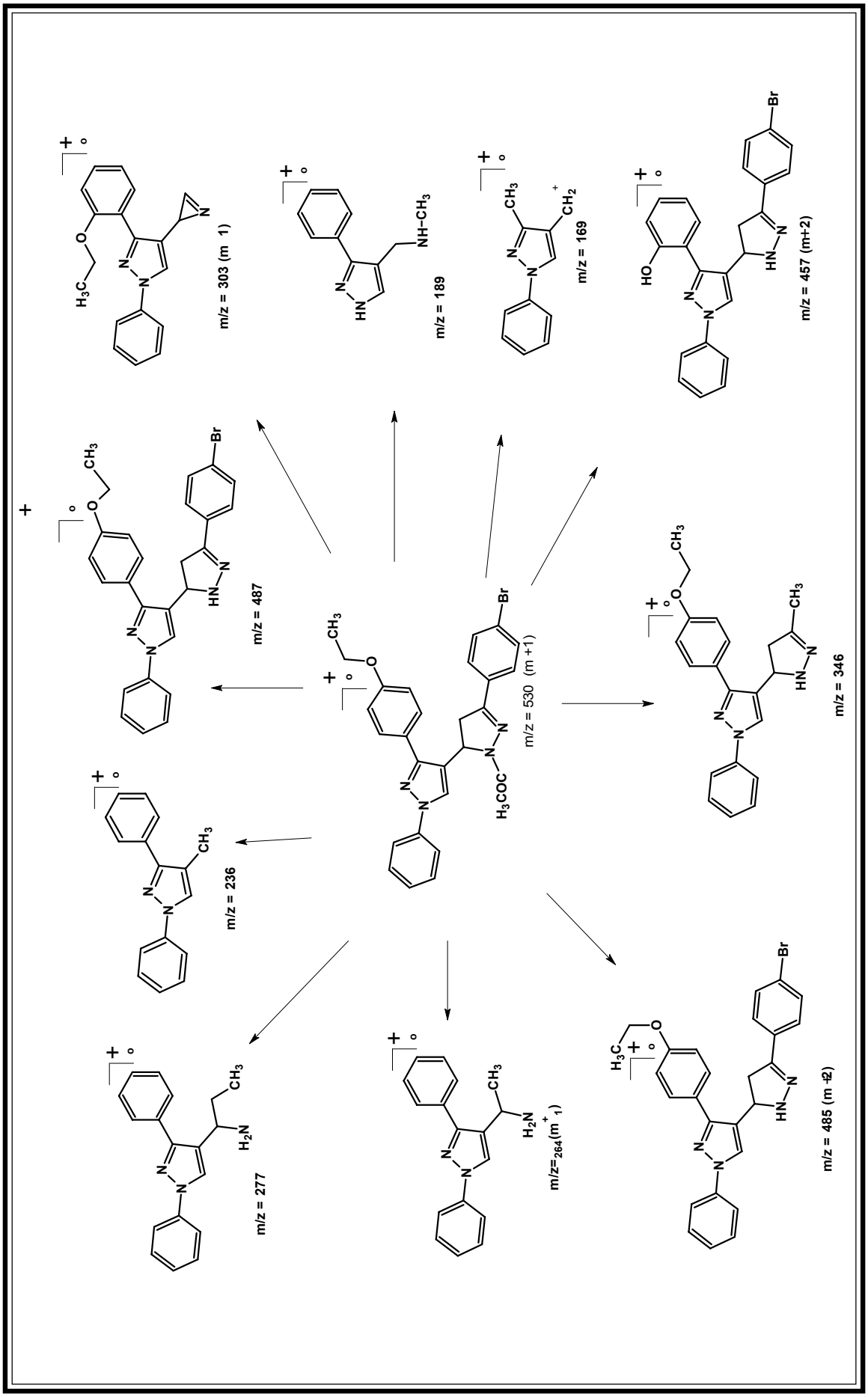
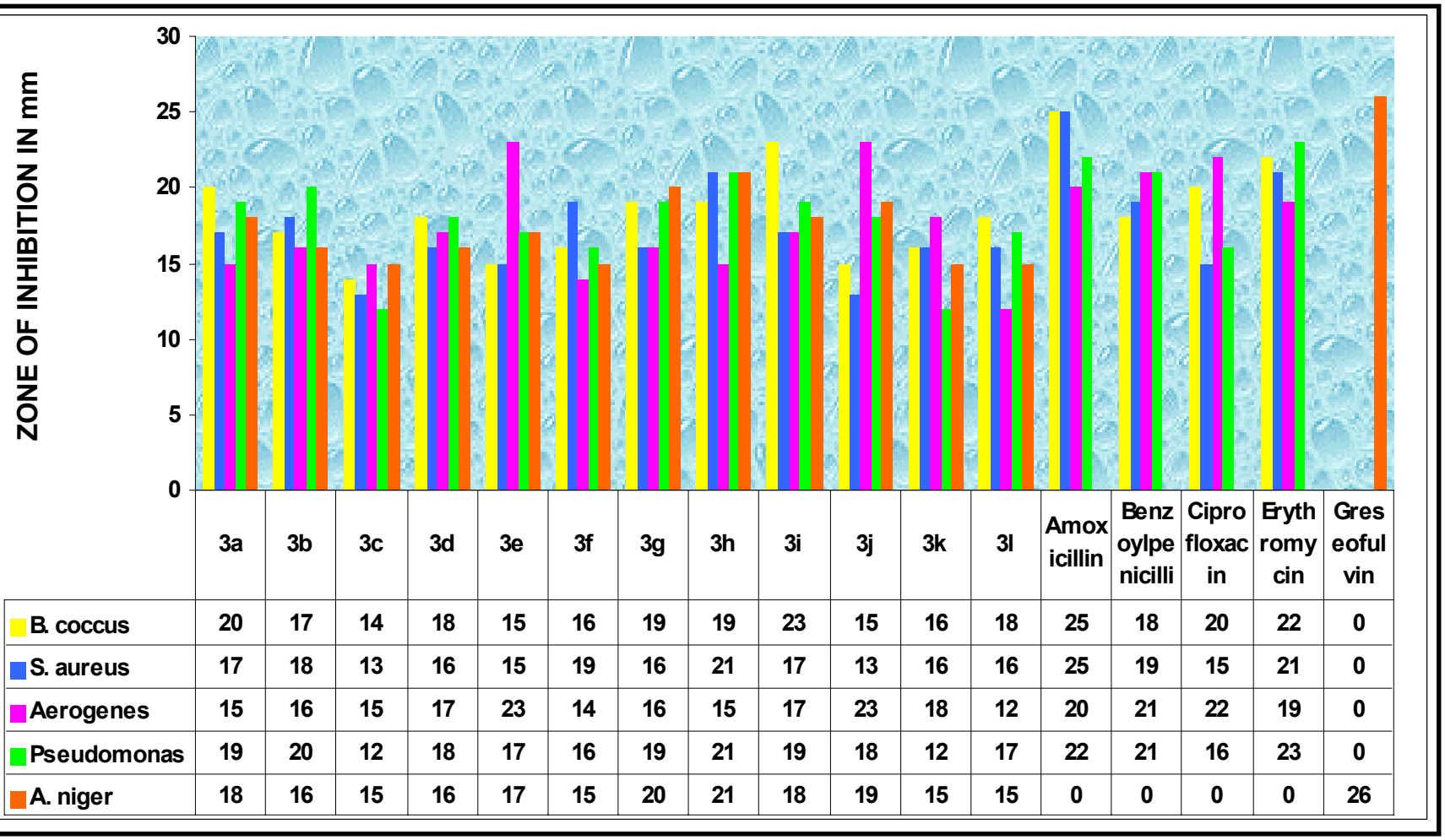

m/z = 530 (m +1)
m/z = 303 (m 1)
m/z = 189
m/z = 169
m/z = 457 (m+2)
m/z = 487
m/z = 346
m/z = 236
m/z = 277
m/z=264(m+ 1)
m/z = 485 (m +2)

TABLE-3 : PHYSICAL CONSTANTS OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)PYRAZOLINES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
3a	C_6H_5-	$C_{28}H_{26}N_4O_2$	450	168	0.68	59	12.44	12.41
3b	4-NH_2-C_6H_4-	$C_{28}H_{27}N_5O_2$	465	121	0.64	60	15.04	15.01
3c	4-Cl-C_6H_4-	$C_{28}H_{25}ClN_4O_2$	484.5	87	0.57	70	11.55	11.49
3d	4-Br-C_6H_4-	$C_{28}H_{25}BrN_4O_2$	529	93	0.60	72	10.58	10.54
3e	4-F-C_6H_4-	$C_{28}H_{25}FN_4O_2$	468	201	0.68	64	11.96	11.91
3f	2-OH-C_6H_4-	$C_{28}H_{26}N_4O_3$	466	185	0.49	58	12.01	11.96
3g	4-OH-C_6H_4-	$C_{28}H_{26}N_4O_3$	466	123	0.55	54	12.01	11.97
3h	4-OCH_3-C_6H_4-	$C_{29}H_{28}N_4O_3$	480	99	0.65	76	11.66	11.61
3i	4-CH_3-C_6H_4-	$C_{29}H_{28}N_4O_2$	464	154	0.53	51	12.06	12.02
3j	3-NO_2-C_6H_4-	$C_{28}H_{25}N_5O_4$	495	111	0.49	74	14.13	14.09
3k	4-NO_2-C_6H_4-	$C_{28}H_{25}N_5O_4$	495	95	0.58	68	14.13	14.07
3l	2-C_4H_3S-	$C_{26}H_{24}N_4O_2S$	456	183	0.62	61	12.27	12.22

*TLC Solvent System : Acetone : Benzene (1 :9)

GRAPHICAL CHART NO. 3 : ANTIMICROBIAL ACTIVITY OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)PYRAZOLINES



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	20	17	14	18	15	16	19	19	23	15	16	18	25	18	20	22	0
S. aureus	17	18	13	16	15	19	16	21	17	13	16	16	25	19	15	21	0
Aerogenes	15	16	15	17	23	14	16	15	17	23	18	12	20	21	22	19	0
Pseudomonas	19	20	12	18	17	16	19	21	19	18	12	17	22	21	16	23	0
A. niger	18	16	15	16	17	15	20	21	18	19	15	15	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

From the experimental data, it has been observed that the compound bearing R=4-tolyl have displayed significant activity against ***B.coccus***. The compound bearing R=4-anisyl have shown good activity against ***S. aureus.***

In case of Gram negative bacterial strains, the compounds with R=4-fluorophenyl and 3-nitrophenyl have shown considerable activity against ***Aerogenes***. The maximum activity was displayed by the compounds bearing R=4-anisyl against ***P.aeruginosa***.

ANTIFUNGAL ACTIVITY

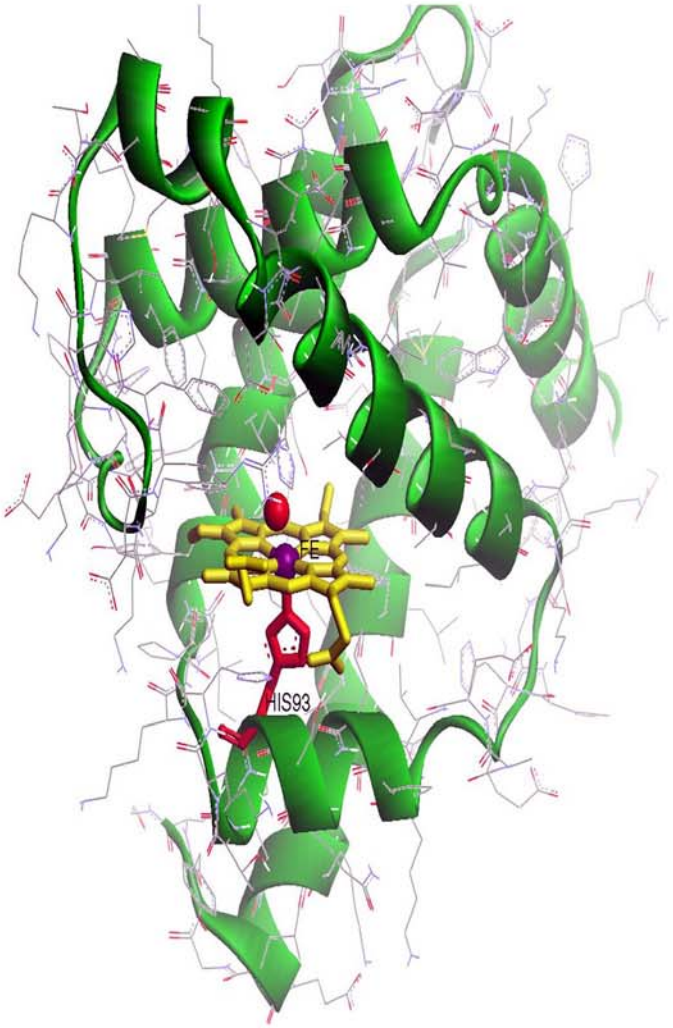
All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=4-anisyl have displayed highest activity against ***A.niger***.

The antimicrobial activity shown by compounds was compared with known antibiotics like amoxycillin, benzoylpenicillin, ciprofloxacin,erythromycin & greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds of type (III) were found to be less active against ***Mycobacterium tuberculosis H37Rv.***

The antitubercular activity data have been compared with standard drug rifampin.



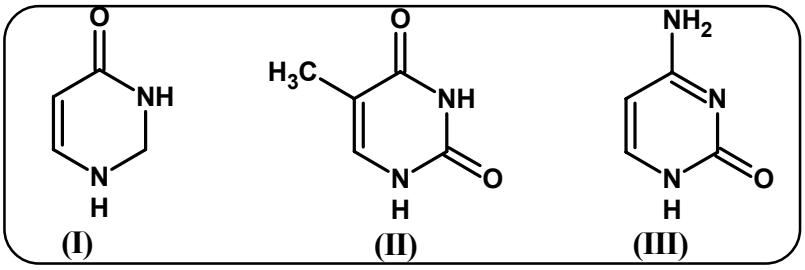
PART-II

STUDIES ON PYRIMIDINES

INTRODUCTION

Pyrimidine is the most important member of all diazines as this ring system occurs widely in living organism. Several analogues of nucleic acid have been used as a compound that interfere with the synthesis and function of nucleic acid,an example is fluorouracil which has been used in cancer treatment.

Pyrimidine derivatives like uracil(I), thymine(II) and cytosine(III) occur widely in nature showing remarkable pharmaceutical importance. Pyrimidine and its derivatives have gained prominence because of their potential pharmaceutical values. Many pyrimidine derivatives play a vital role in many physicological action, some of the building blocks of DNA and RNA.

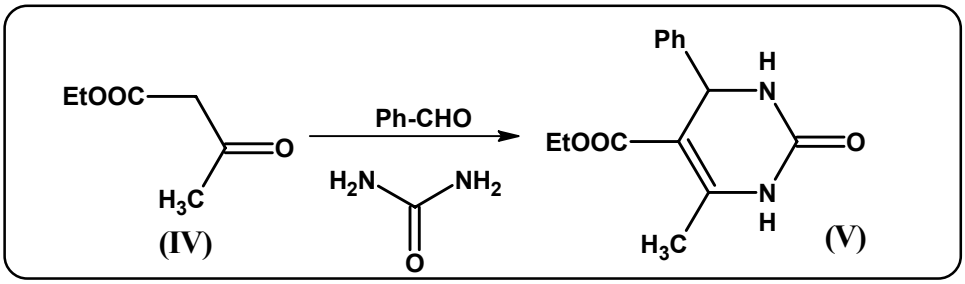


Pyrimidine is considered to be a resonance hybrid of charged and uncharged cannonical structures, its resonance energy has been found to be more than benzene or pyridine. The naturally occuring pyrimidine derivative was first isolated by Grabial and Colman in 1870, and its structure was confirmed in 1953 as 5-b-gluco-pyranoside of divicine.

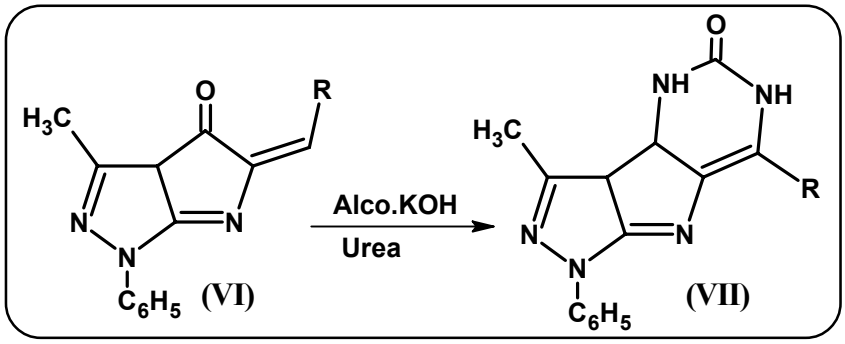
SYNTHETIC ASPECTS

Different methods for the synthesis of pyrimidinones have been cited in the literature.[113]

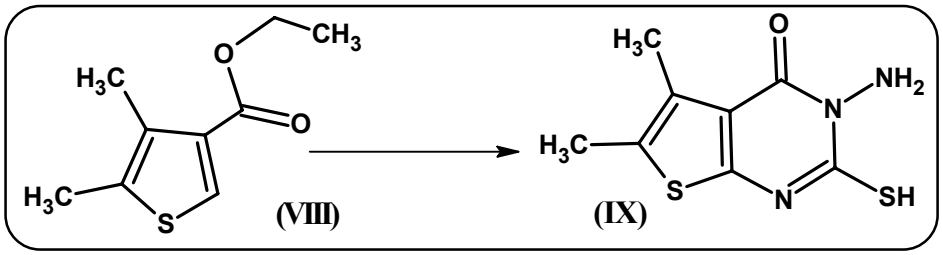
1. Biginelli[114] investigated that condensation of aromatic aldehyde with b-ketoester and urea yield the pyrimidine derivatives.



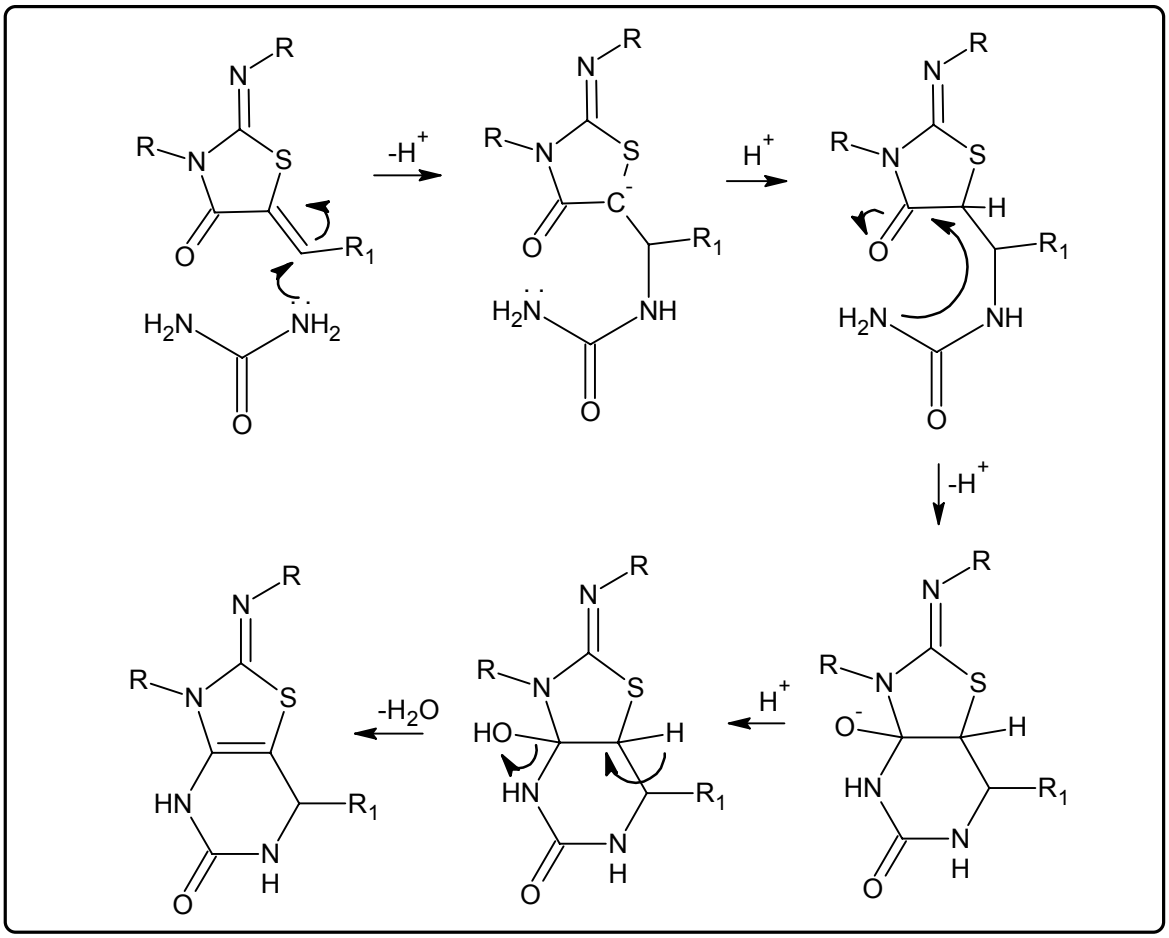
2. Hussain Ali Saleiman et.al.[115] have prepared oxopyrimidine derivatives(VII) by using urea in alcoholic KOH.



3. V. Alagarsamy et. al.[116] have prepared pyrimidines from thiosemicarbazide.



MECHANISM



THERAPEUTIC IMPORTANCE

Pyrimidine derivatives have been proved to be of great importance in exhibiting and enhancing the biological activities such as,

(a) Antitumor[117]

(b) Carcinostatic[118]

(c) Antiinflammatory and anticonvulsant[119,120]

(d) Antimalarial[121]

(e) Antithyroid[122]

(f) Anthelmintic[123]

(g) AntiHIV[124,125]

(h) Antilishmential[126]

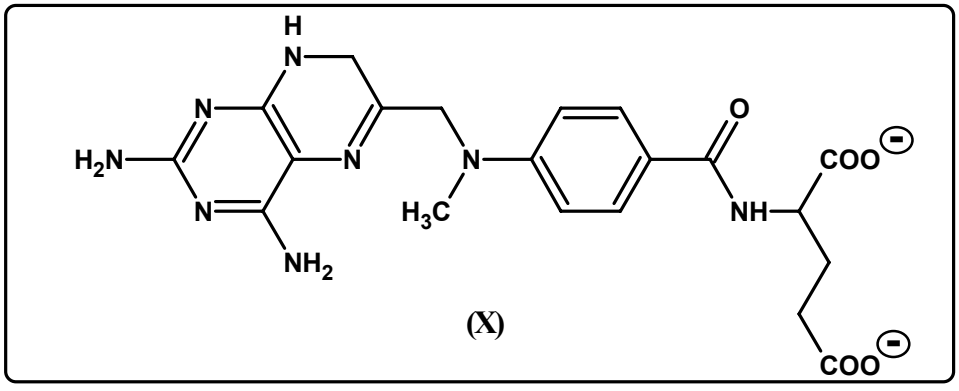
(i) Antiviral[127]

(j) Antimicrobial[128]

(k) Herbicidal[129]

(l) Antagonists[130-132]

Baraldi P. G. et. al.[133] have discovered triazolo [1,5-c] pyrimidine derivatives as a new class of A_2A adenosine receptor antagonists.Azaryan et. al.[134] have synthesised pyrimidine diones as antitumor agent. Krivongov and co-workers[135] have synthesised pyrimidinone derivatives possessing immunotropic and antiinflammatory activity. Timothy and co-workers[136] have suggested imidazolyl pyrimidinones as antiviral.Balis F. M. et. al.[137] has investigated pyrimidines (X) used in the treatment of leukamia in childhood.

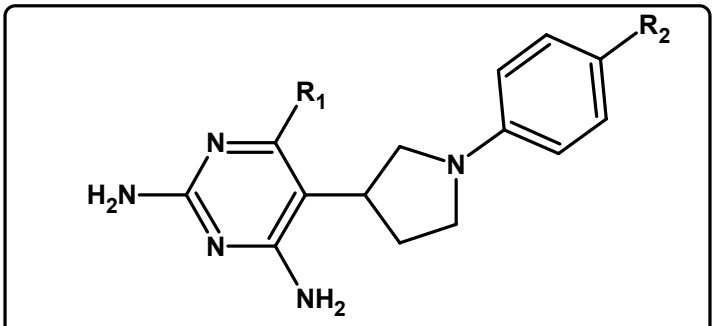


(X)

Amuti Kofies et. al.[138] have suggested pyrimidinones as herbicidal and plant growth regulators. K. Mogilaiah et. al.[139] have prepared spiropyrimidinones as antibacterial. Mona Mahran and co-workers[140] have reported pyrimidine derivatives

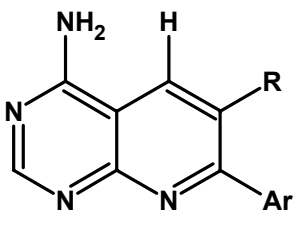
as potent antimicrobial and antitumor agent.Bruce M. A & co-workers[141] have prepared the dihydro pyrimidinones as NPY antagonist.Antitumor activity of new pyrimidinone of sesquiterpene lactones has been found by Angelina Quintero et. al.[142] Barbuliene M. M. et. al.[143] have synthesised pyrimidinones as antiinflammatory agent.

El-Agrody A. M. et.al.[144] have studied antimirobial activity of pyrimidine derivatives.Patricia F. F. et. al.[145] have synthesised and screened for their leukocyte functions inhibitor activity. Dumas Jacques et. al.[146] have synthesised pyrimidinones and tested their hyperproliferative disorder activity.Tsann-Long Su et. al.[147] have reported pyrimidines (XI) as antitumor agents.

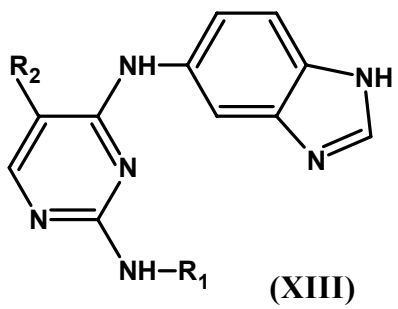


(XI) $R_1 = NH_2$, OH; R_2 = H, Me, NO_2, CN, F

Richard J. Perneu et. al.[148] have discovered pyrimidine derivatives (XII) as adenosine kinase inhibitors. Sharad Verma et. al.[149] have prepared pyrimidines (XIII) as cyclin-dependent kinase inhibitors.

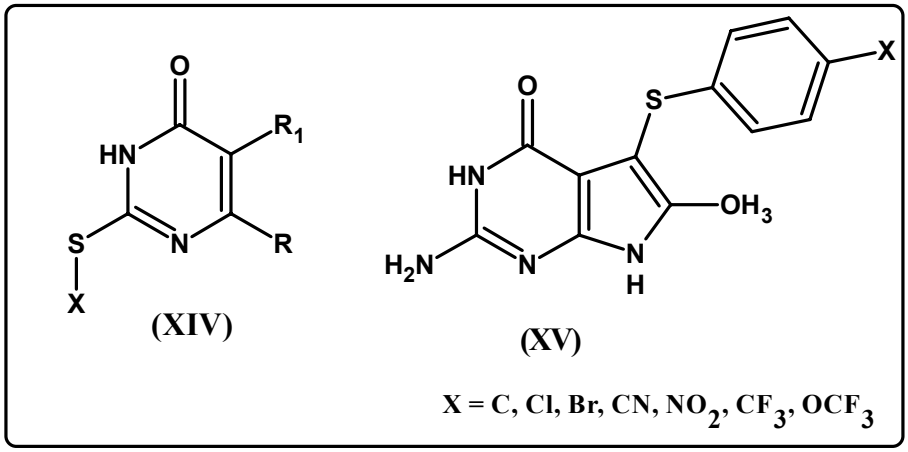


(XII) R = Aryl / Alkyl

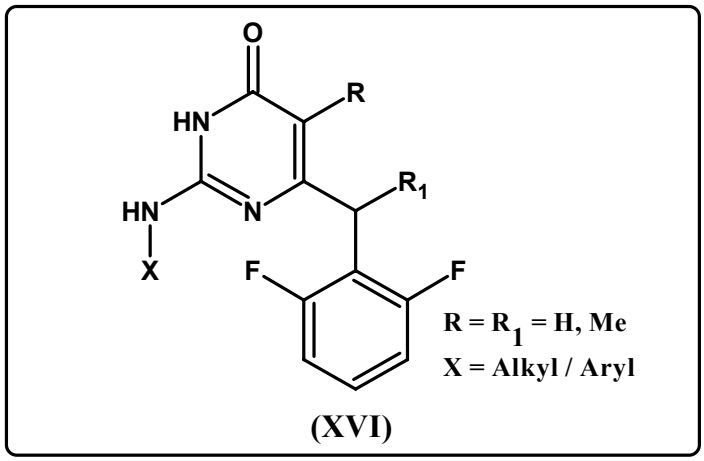


(XIII)

Viney Hather & A. K. Madan[150] have prepared pyrimidinones(XIV) as anti-HIV agents.Aleem Gangiee & co-workers[151] have prepared pyrimidinone derivatives (XV) as non classical antitolate inhibitors of thymidylate synthase.



Recently, Antonello Mai et. al.[152] have synthesised pyrimidine derivative (XVI) as non-nucleoside reverse transcriptase inhibitors.Maria T. Cocco and co-workers[153] have synthesised hydrazinopyrimidine-5-carbonitrile derivatives and reported their antitumor activity.Rudolf Waelchli et. al.[154] have synthesised pyrimidine derivatives as IKK inhibitors. Naveen Chandra and co-workers[155] have synthesised some aryl substituted terpenyl pyrimidines and reported their antileishmanial activity.



Literature survey reveals that pyrimidine derivatives possess potential drug activity. Looking to the diversified biological activity, it appeared of interest to synthesize some pyrimidines bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance.. These studies described in following parts.

ECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2 ARYLIMINO-3,N-ARYL-5-[1,'N-PHENYL-3'-*P* ETHOXYPHENYL)-4'-PYRAZOLYL-METHINO]-4 THIAZOLIDINONES

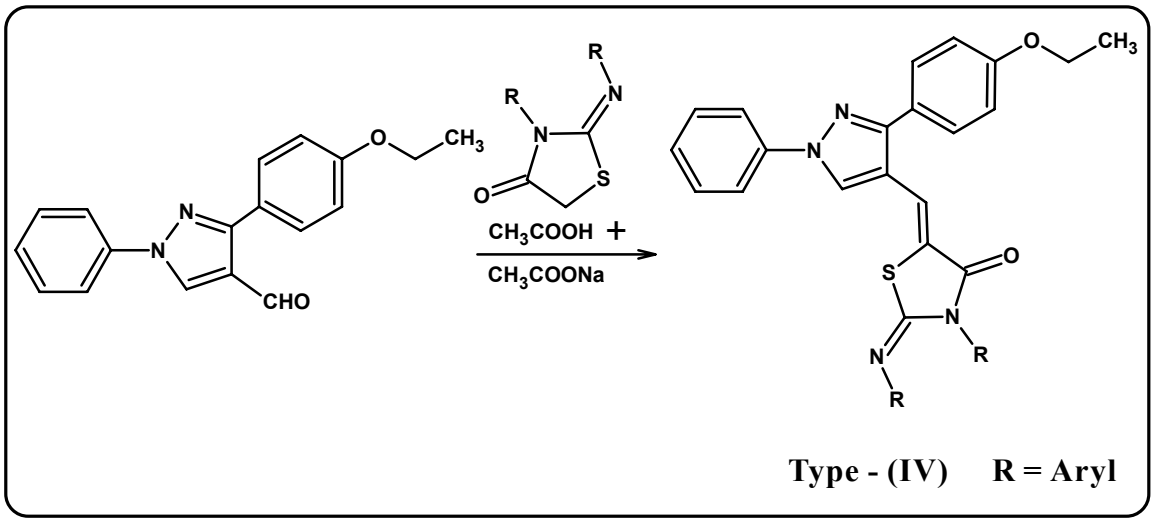
SECTON- II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-*P*-ETHOXYPHENYL-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDROTHIAZOLIDINO-[4,5-e]-PYRIMIDINES

SECTON- II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-*P*-ETHOXYPHENY-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDROTHIAZOLIDINO-[4,5-e]-PYRIMIDINES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

Recently much interest has been foucused on the synthesis and biodynamic activities of arylidene and it is a good synthon for various heterocyclic rings. With a view to obtaining compounds having better therapeutic activities, we have synthesised 2-arylimino-3-N-aryl-5-[1',N-phenyl-3'-(*p*-ethoxyphenyl)-4'-pyrazol methino]-4-thiazolidinones by the condensation of pyrazole aldehyde with various thiazolidinone derivatives.

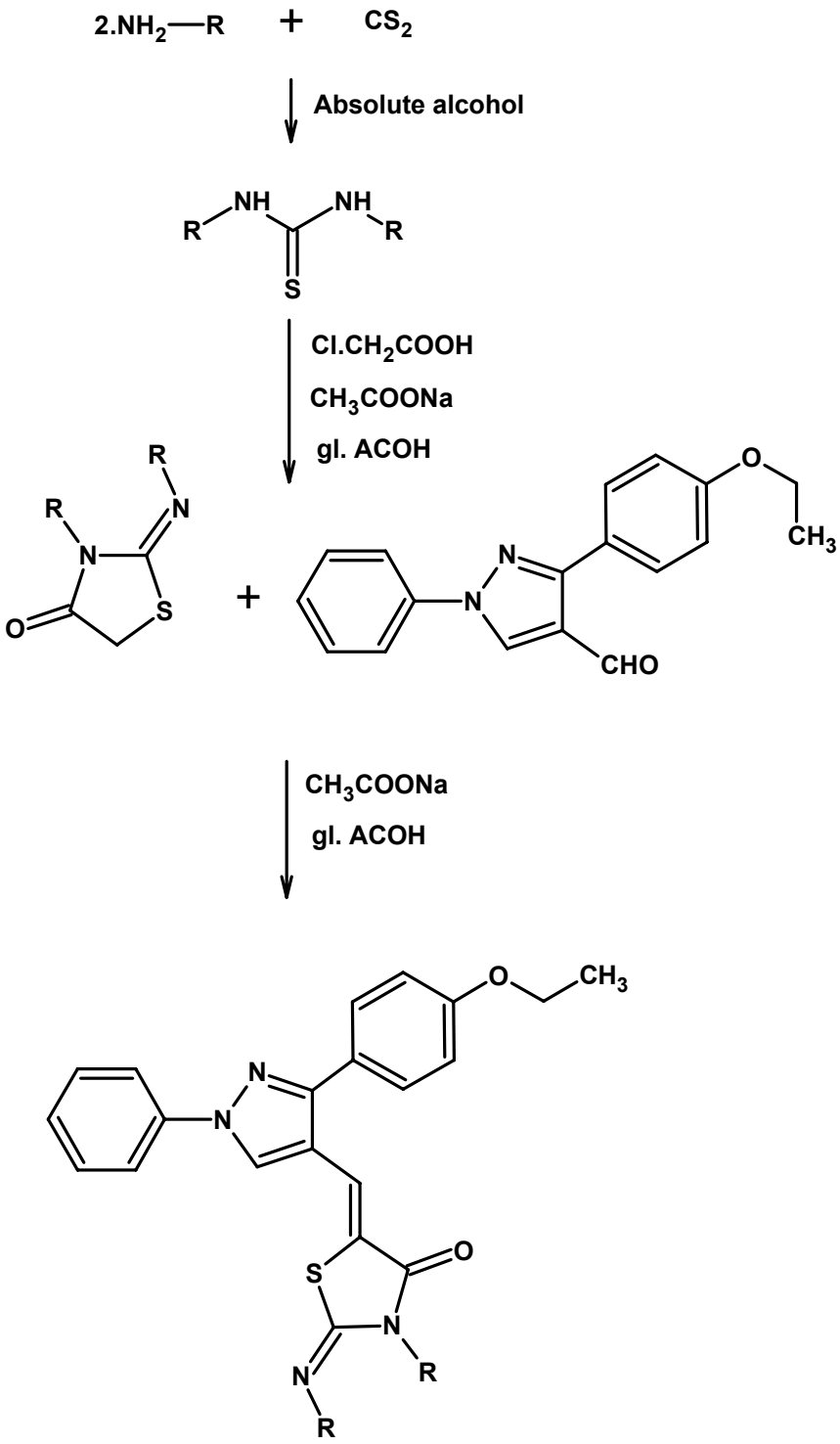


Type - (IV) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (IV) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

[A] Preparation of N^1, N^3-Bis-*p*-anisyl thiourea[156]

In a round bottom flask, a mixture of *p*-fluroaniline(0.2M), carbon disulphide (7ml, 0.01M) and absolute alcohol was heated for 5-6 hrs. at temp 40^{O}C. On completion of reaction, the excess of carbon disulphide and alcohol was removed by distillation. The product was treated with hydrochloric acid to remove excess of amine present and crude product was isolated and crystallised from ethanol. m.p.203 ^{O}C.

[B] Preparation of 2-*p*-Fluorophenylimino-3-*p*-fluoroaniline-5H-4 thiazolidinones[157]

A solution of N^1, N^3-bis-*p*-fluroaniline thiourea (0.01M) and chloroacetic acid (0.94g, 0.01M) in glacial acetic acid (15 ml) was refluxed with fused sodium acetate (1.25g, 0.015M) for 8 hrs. The reaction product was poured in water, kept overnight, crude product was isolated and crystallised from ethanol. m.p. 209^{O}C.

[C] Preparation of 2-(*p*-Fluorophenylimino)-3.N-(*p*-flurophenyl)-5-[1',N-phenyl-3'-(*p*-ethoxyphenyl)-4'-pyrazolyl methino]-4-thiazolidinone

A mixture of 2-(*p*-fluroanilineimino)-3-*p*-fluroaniline-5H-4-thiazolidinone (3.36g, 0.01M) 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl pyrazole (2.92g, 0.01M) and fused sodium acetate (1.25g, 0.015M) was refluxed in glacial acetic acid (15 ml) for 9-10 hrs. at temp 120^{O}C. cooled, poured into water and treated with ammonia to remove excess of glacial acetic acid. The product was isolated and crystallised from ethanol. yield 72% m.p. 186^{O}C ($C_{33}H_{24}F_2N_4O_2S$: Found : C, 68.50%; H, 4.18%; N, 9.68% Requires : C, 68.44%; H, 4.12%; N, 9.63%).

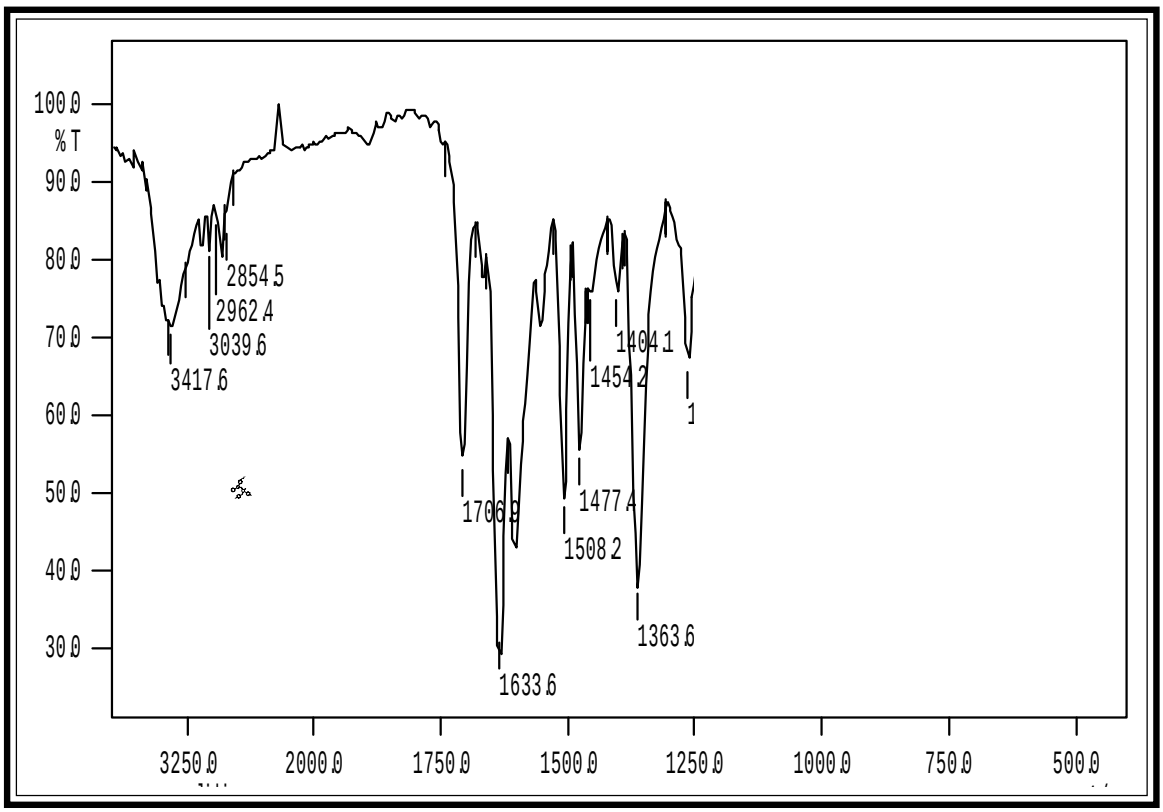
TLC solvent system : Acetone : Benzene (2 : 8).

Similarly other substituted thiazolidinones have been prepared. The physical data are recorded in Table No. 4.

[D] Therapeutic activity of 2-Arylimino-3,N-aryl-5-[1',N-phenyl-3'-(*p*-ethoxyphenyl)-4'-pyrazolylmethino]-4-thiazolidinones

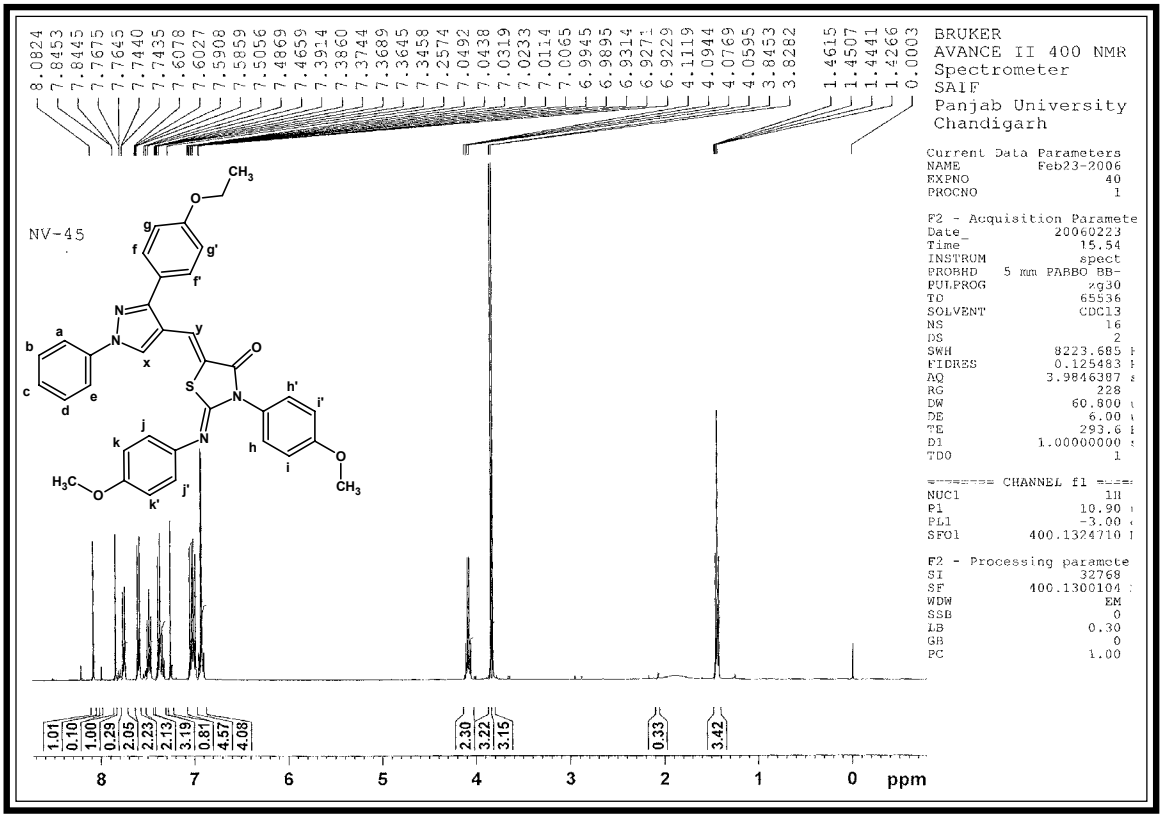
Antimicrobial testing was carried out as described in [a] Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No.4.

IR SPECTRAL STUDY OF 2-(*p*-FLUOROPHENYLIMINO)-3,N-(*p*-FLUOROPHENYL)-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'PYRAZOLYLMETHINO]-4-THIAZOLIDINONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophd[redacted] Frequency range : 4000-400 cm^{-1} (KBr disc.)

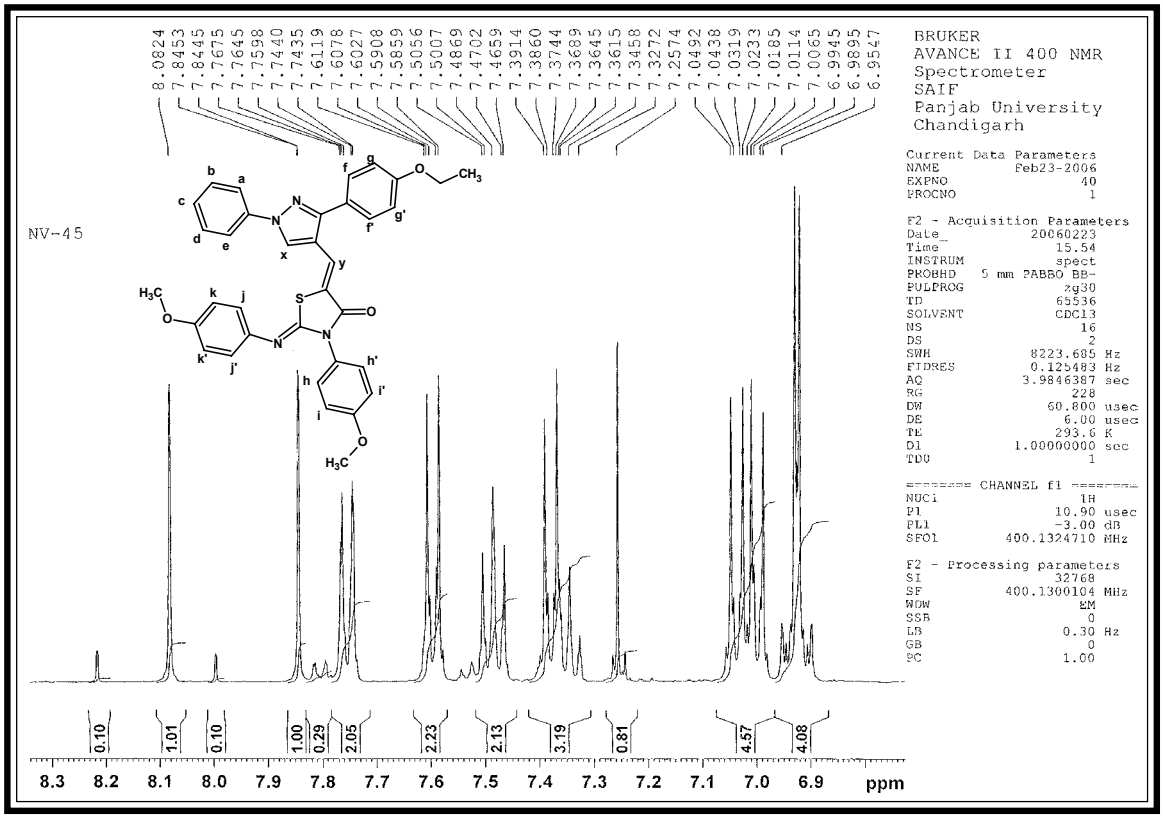
PMR SPECTRAL STUDY OF 2-(*p*-ANISYLIMINO)-3,N-(*p*-ANISYL)-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'PYRAZOLYLMETHINO]-4-THIAZOLIDINONE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.42-1.46	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.81
2.	3.84-3.82	6H	singlet	$-OCH_3$	-
3.	4.05-4.11	2H	quartet	$-O\underline{CH}_2CH_3$	J_{CH_2}=7.0
4.	6.92-6.98	4H	multiplet	Ar-$H_{hh'}$,Ar-$H_{gg'}$	-
5.	6.98-7.01	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.7
6.	7.02-7.04	2H	doublet	Ar-$H_{kk'}$	J_{kj}=8.7
7.	7.36-7.38	3H	multiplet	Ar-$H_{a,c,e}$	-
8.	7.46-7.50	2H	triplet	Ar-H_{bd}	-
9.	7.58-7.60	2H	double	Ar-$H_{jj'}$	J_{jk}=8.7
10.	7.74-7.76	2H	double	Ar-$H_{ff'}$	J_{fg}=8.2
11.	7.84	1H	singlet	CH_y	-
12.	8.08	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION

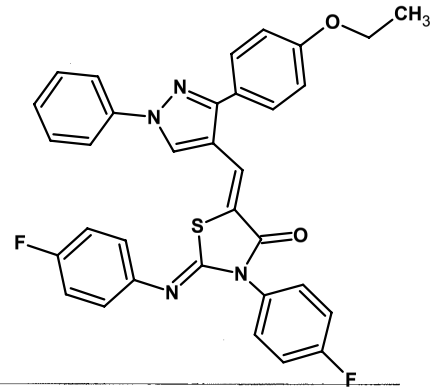


IR SPECTRAL STUDY OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

Sr. No.	R	C=O str.
4a	C_6H_5-	1708
4b	4-OCH_3-C_6H_4-	1709
4c	3-OCH_3-C_6H_4-	1710
4d	4-CH_3-C_6H_4-	1706
4e	3-CH_3-C_6H_4-	1714
4f	4-OH-C_6H_4-	1705
4g	4-F-C_6H_4-	1706
4h	4-Cl-C_6H_4-	1710
4i	4-Br-C_6H_4-	1715
4j	3,4-$(Cl)_2$-C_6H_3-	1712
4k	4-NO_2-C_6H_4-	1710
4l	3-NO_2-C_6H_4-	1712

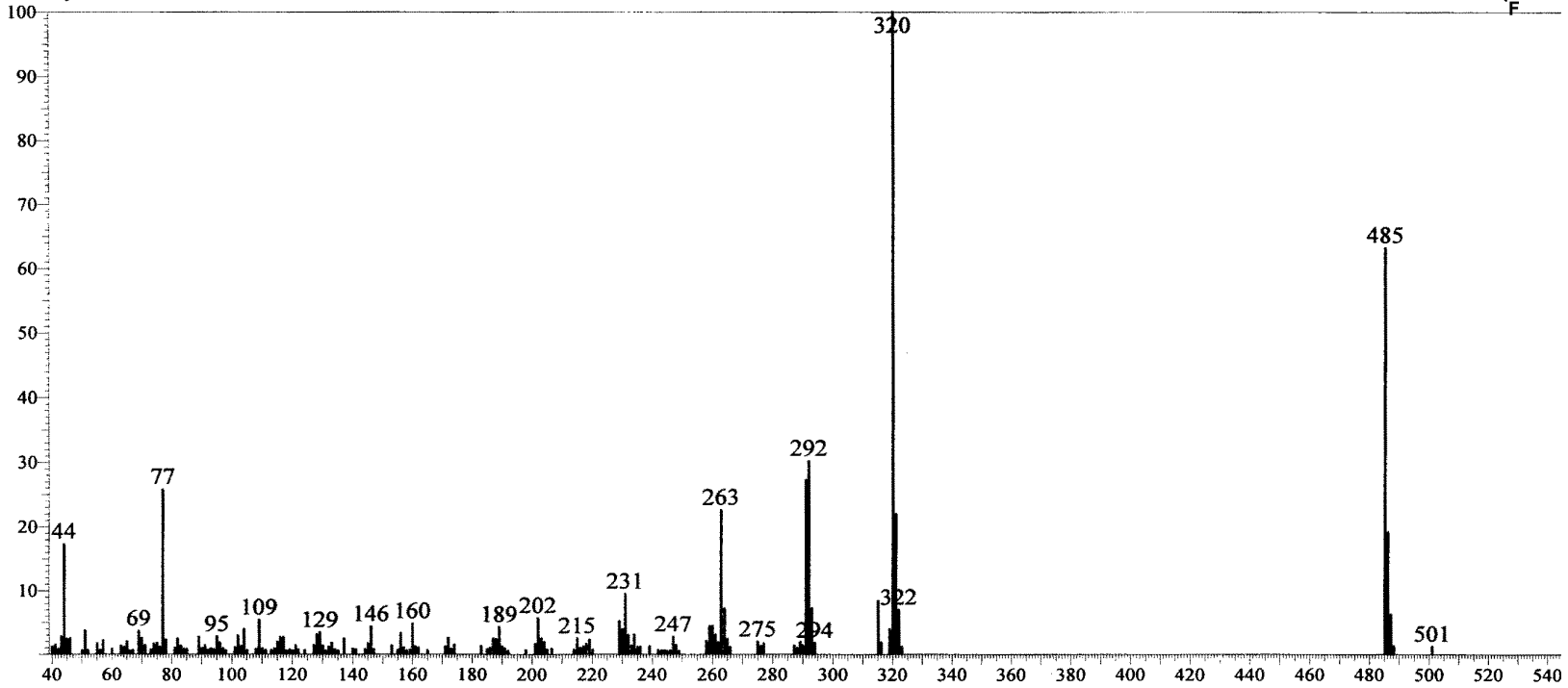
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information



Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 2/2/2006 4:09:15 PM
Sample Name : NV-25
Sample ID : NV-25
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-25.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:7.6(Scan#:877)
MassPeaks:169 BasePeak:320(195379)
RawMode:Single 7.6(877)
BG Mode:None
intensity



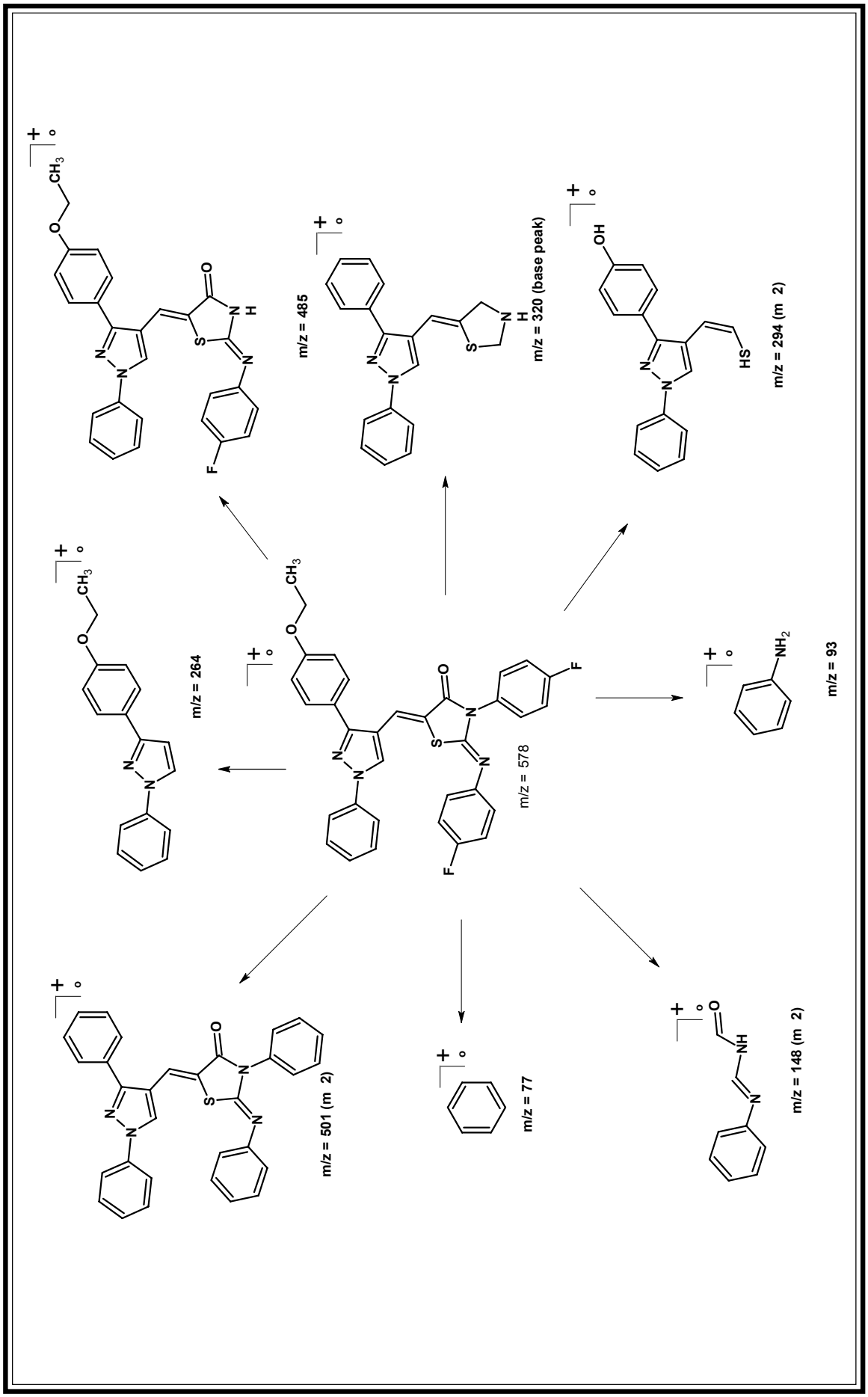
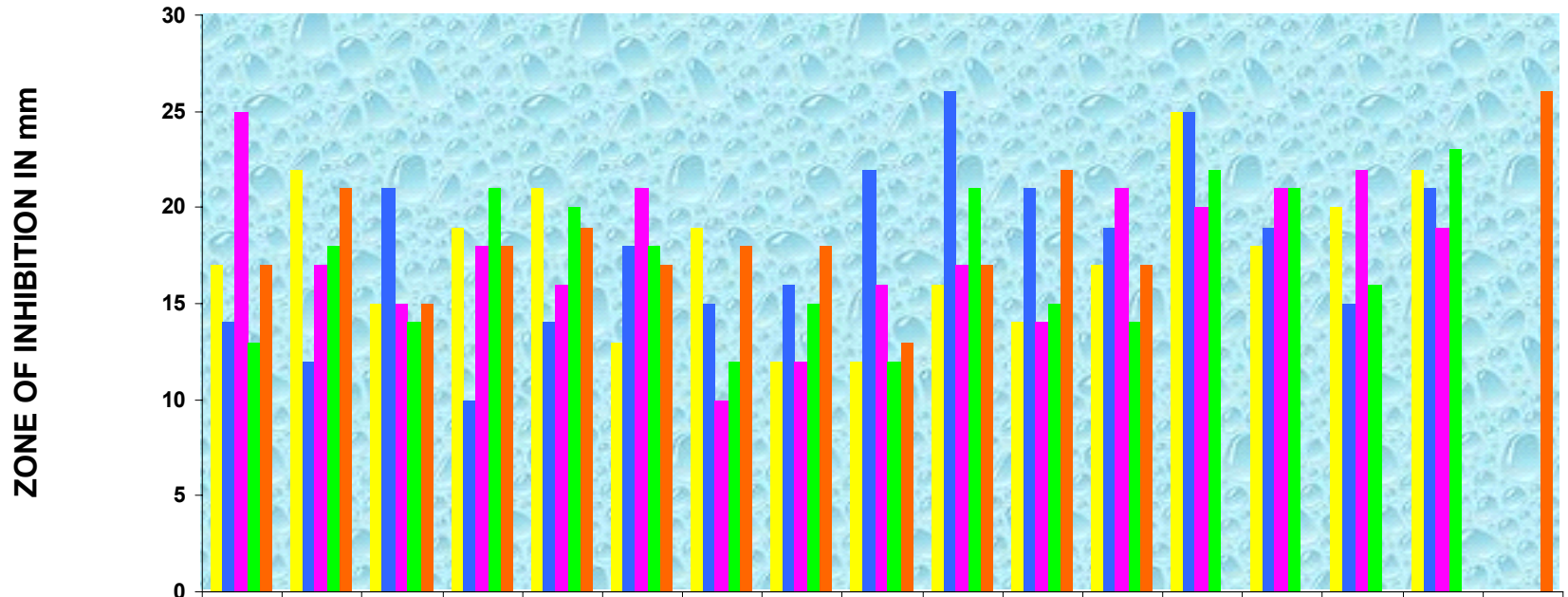

m/z = 578
m/z = 485
m/z = 320 (base peak)
m/z = 294 (m 2)
m/z = 264
m/z = 93
m/z = 501 (m 2)
m/z = 77
m/z = 148 (m 2)

TABLE-4 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

Sr. No.	R Formula	Molecular Weight	Molecular ^{o}C	M. P Value	Rf* %	Yield Calcd.	% of Nitrogen Found	
1	2	3	4	5	6	7	8	9
4a	C_6H_5-	$C_{33}H_{26}N_4O_2S$	542	174	0.59	68	10.32	10.28
4b	4-OCH_3-C_6H_4-	$C_{35}H_{30}N_4O_4S$	602	158	0.61	59	9.30	9.26
4c	3-OCH_3-C_6H_4-	$C_{35}H_{30}N_4O_4S$	602	205	0.62	71	9.30	9.25
4d	4-CH_3-C_6H_4-	$C_{35}H_{30}N_4O_2S$	570	145	0.58	68	9.82	9.78
4e	3-CH_3-C_6H_4-	$C_{35}H_{30}N_4O_2S$	570	202	0.64	58	9.82	9.78
4f	4-OH-C_6H_4-	$C_{33}H_{26}N_4O_4S$	574	147	0.52	71	9.75	9.70
4g	4-F-C_6H_4-	$C_{33}H_{24}F_2N_4O_2S$	578	186	0.58	72	9.68	9.63
4h	4-Cl-C_6H_4-	$C_{33}H_{24}Cl_2N_4O_2S$	611	139	0.68	69	9.16	9.13
4i	4-Br-C_6H_4-	$C_{33}H_{24}Br_2N_4O_2S$	700	229	0.64	55	8.00	7.97
4j	3,4-$(Cl)_2$-C_6H_3-	$C_{33}H_{22}Cl_4N_4O_2S$	680	201	0.53	61	8.23	8.19
4k	4-NO_2-C_6H_4-	$C_{33}H_{24}N_6O_6S$	632	210	0.55	68	13.28	13.25
4l	3-NO_2-C_6H_4-	$C_{33}H_{24}N_6O_6S$	632	299	0.57	76	13.28	13.24

*TLC Solvent System : Acetone: Benzene (2 : 8)

GRAPHICAL CHART NO. 4 : ANTIMICROBIAL ACTIVITY OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL 3'-(*p*- ETHOXYPHENYL)-4'-PYRAZOLYLMETHINO]-4-THIAZOLIDINONES



	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Greseofulvin
B. coccus	17	22	15	19	21	13	19	12	12	16	14	17	25	18	20	22	0
S. aureus	14	12	21	10	14	18	15	16	22	26	21	19	25	19	15	21	0
E. aerogenes	25	17	15	18	16	21	10	12	16	17	14	21	20	21	22	19	0
P. aeruginosa	13	18	14	21	20	18	12	15	12	21	15	14	22	21	16	23	0
A. niger	17	21	15	18	19	17	18	18	13	17	22	17	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been concluded from the experimental data that the compounds bearing R=4-anisyl and 3-tolyl have displayed good activity against ***B.coccus***. The compounds bearing R=3-anisyl,4-bromophenyl, 3,4-dichlorophenyl and 4-nitrophenyl have shown considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains all the compounds were inactive against ***E.aerogenes*** except the compound bearing R=phenyl,3-nitrophenyl and 4-hydroxyphenyl. While the compounds bearing R=4-tolyl, 3,4-dichlorophenyl showed significant activity against ***P.aeruginosa***.

ANTIFUNGAL ACTIVITY

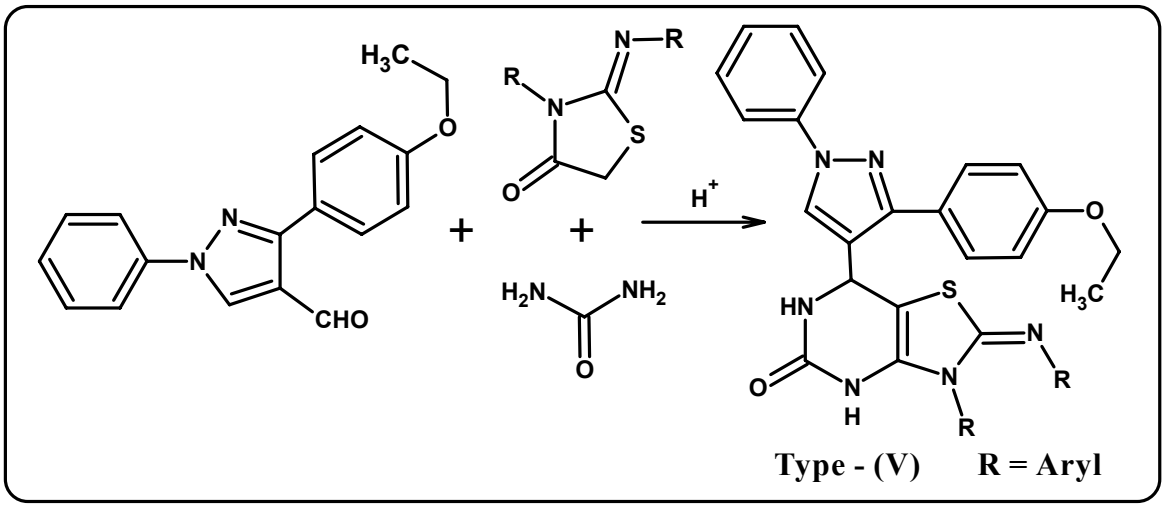
All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=4-anisyl and 4-nitrophenyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drug viz.amoxicillin,benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES

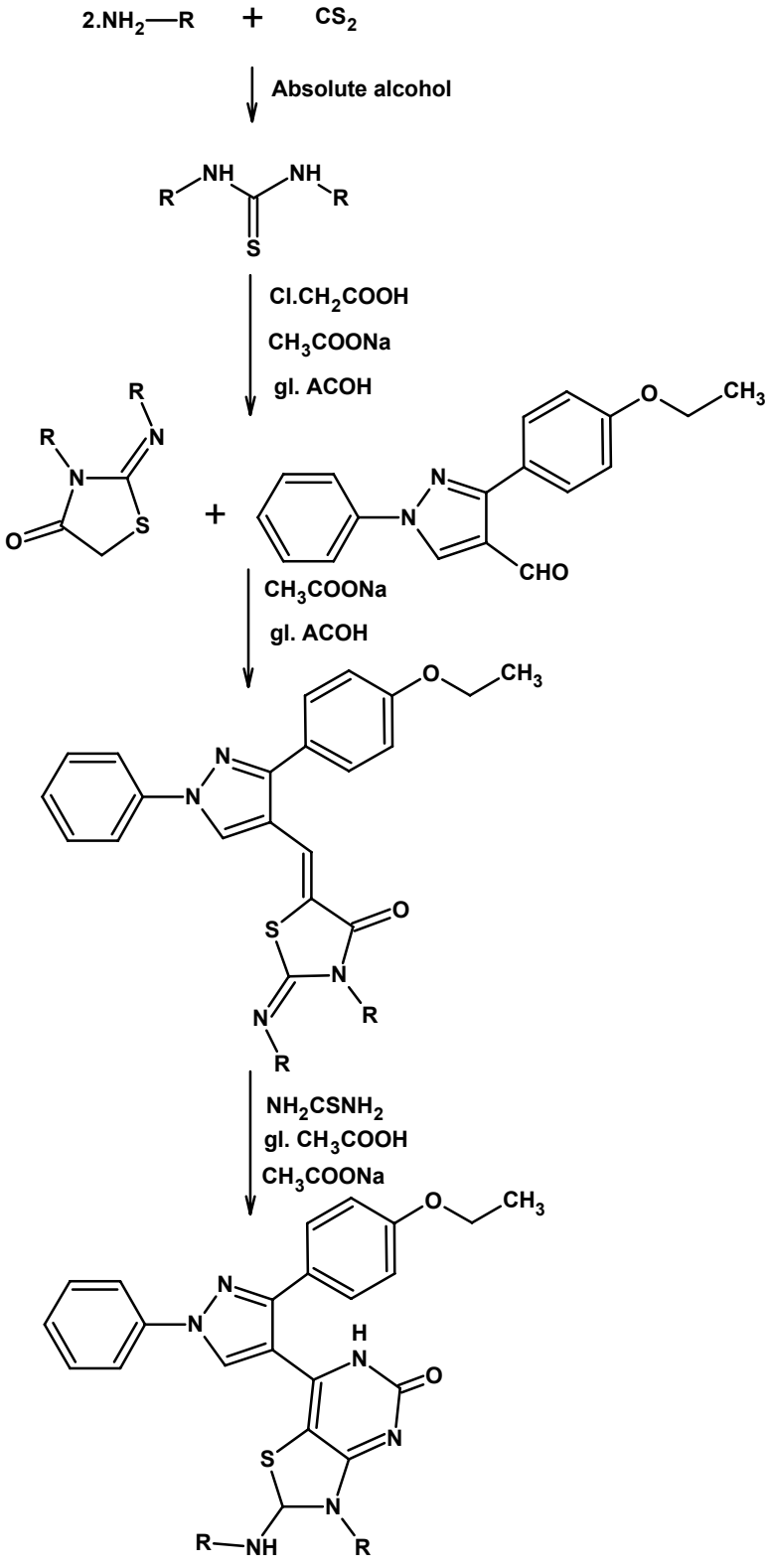
Many pyrimidinone derivatives are associated with diversified biological properties. It was thought of interest that a pyrimidinone ring couple to pyrazole nucleus and thiazolidinone nucleus, the resulting compounds may possess significant biological potency.Pyrimidinones of type (V) have been prepared by the condensation of 2-arylimino-3-aryl-5H-4-thiazolidinone, 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl-pyrazole and urea in glacial acetic acid with fused sodium acetate.



The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (V)

R = Aryl

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDRO-THIAZOLIDINO-[4,5-e]-PYRIMIDINES

[A] Preparation of 2-*p*-Fluorophenylimino-3-*p*-fluorophenyl-5H-4-thiazolidinone[157]

See, Part-II, Section-I (B)

[B] Preparation of 6-(*p*-Fluorophenylimino)-7,N-(*p*-fluoropheny)-2-oxo-4-(1',N-phenyl-3'-(*p*-ethoxyphenyl-pyrazol-4'-yl)-1,2,3,4 tetrahydro thiazolidino-[4,5-e]-pyrimidine

A mixture of 2-*p*-fluorophenylimino-3-(*p*-fluorophenyl)-5H-4-thiazolidinone (3.36g, 0.01M), 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl-pyrazole (2.92g, 0.01M)and urea (0.60g, 0.01M) were mixed in glacial acetic acid (20 ml) with fused sodium acetate(1.25gm, 0.015M). The reaction mixture was refluxed for 10 hrs. cooled, poured into crushed ice. The product was isolated and crystallised from methanol-DMF. Yield 72%, m.p. 232^{o}C ($C_{34}H_{26}F_2N_6O_2S$, Found : C, 65.99%; H, 4.22%; N, 13.54% Requires : C, 65.94%; H,4.17%; N, 13.48%;).

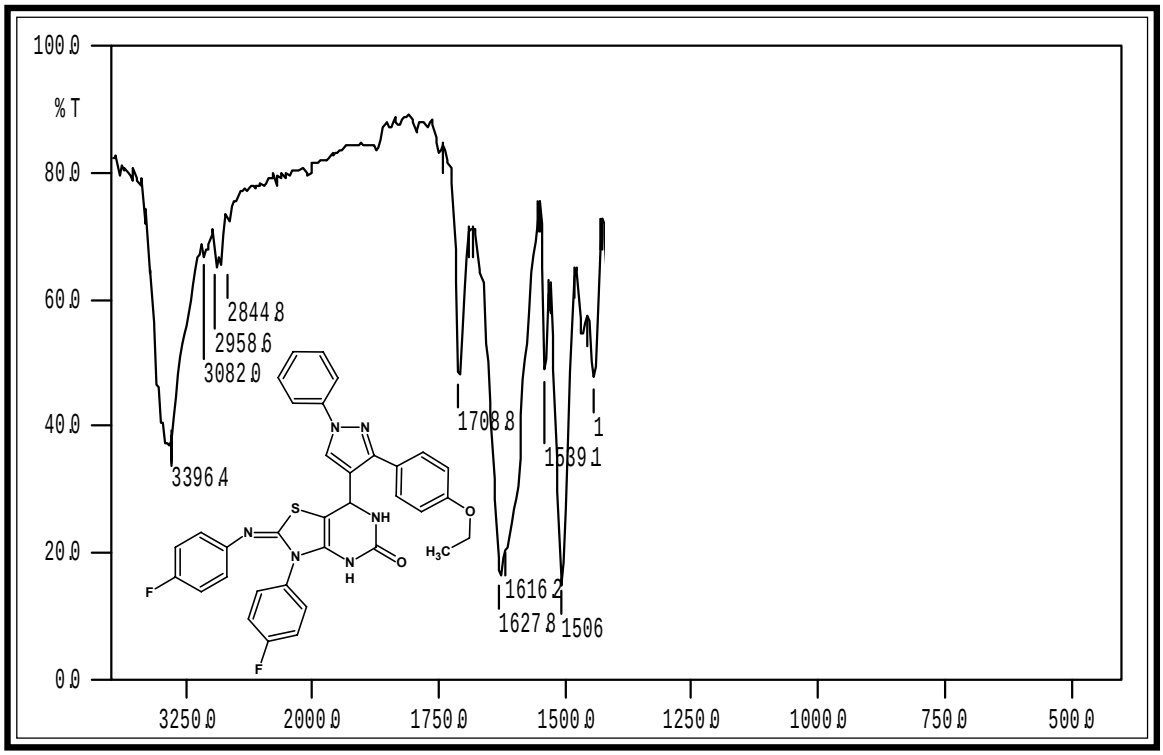
TLC solvent system : Ethyl acetate : Hexane (1.8 : 8.2).

Similarly other pyrimidines were prepared. The physical data are recorded in Table No. 5.

[C] Therapeutical activity of 6-Arylimino-7,N-aryl-2-oxo-4-[1',N-phenyl-3'-(*p*-ethoxyphenyl)-pyrazol-4'-yl]-1,2,3,4-tetrahydro-thiazolidino-(4,5-e)-pyrimidines

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 5.

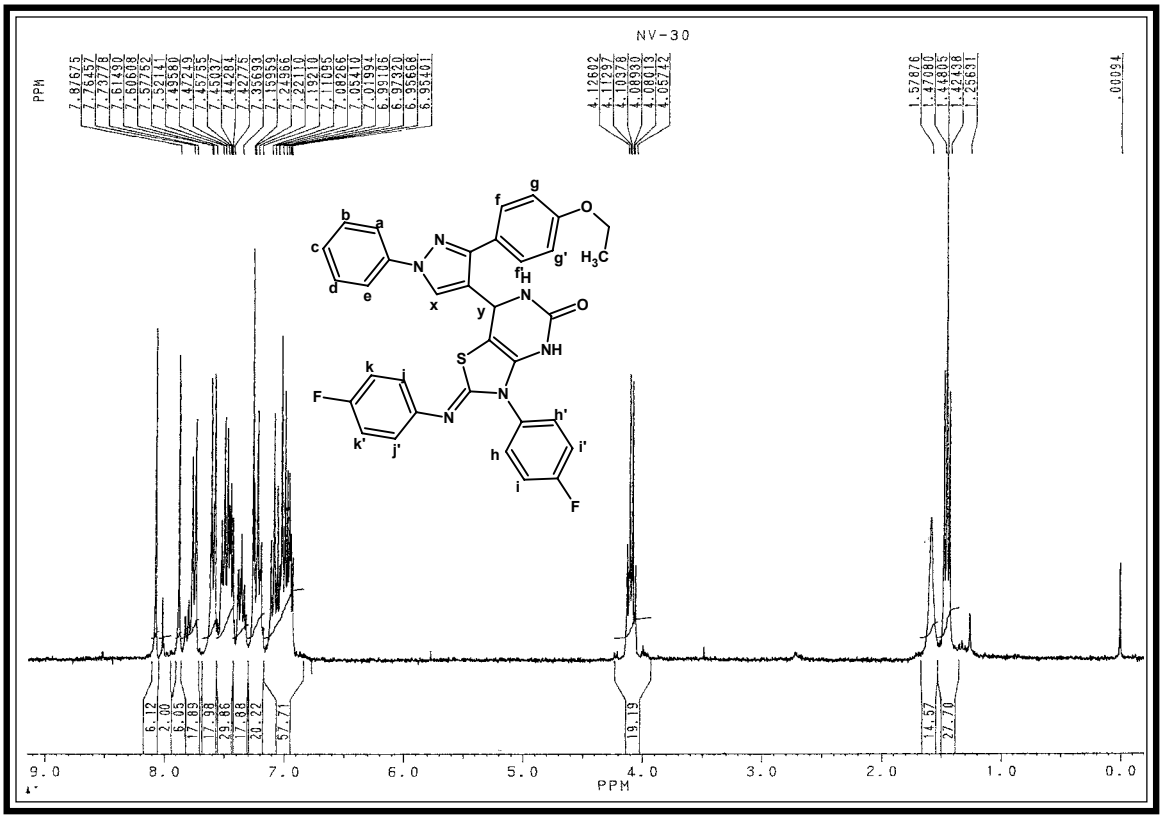
IR SPECTRAL STUDY OF 6-*p*-FLUOROPHENYLIMINO-7,N-*p*-FLUOROPHENYL-2-OXO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2958	2975-2950	413
-CH_3	C-H str. (sym.)	2844	2880-2860	
	C-H i.p.def. (asym.)	1415	1470-1435	
Aromatic	C-H str.	3082	3080-3030	
	C=C str.	1539	1585-1480	414
	C-H i.p. def.	1151	1125-1090	
	C-H o.o.p. def	831	835-810	
Pyrazole	C=N str.	1616	1630-1590	415
moiety	C-N str.	1224	1230-1020	
	C-F str.	758	830-560	413
Ether	C-O-C str. (asym.)	1249	1275-1200	413
	C-O-C str. (sym.)	1028	1075-1020	
Pyrimidine	C=O str.	1708	1750-1600	416
ring	N-H str.	3396	3500-3350	
	C=N str.	1627	1650-1550	
	C-S-C str.	688	700-600	

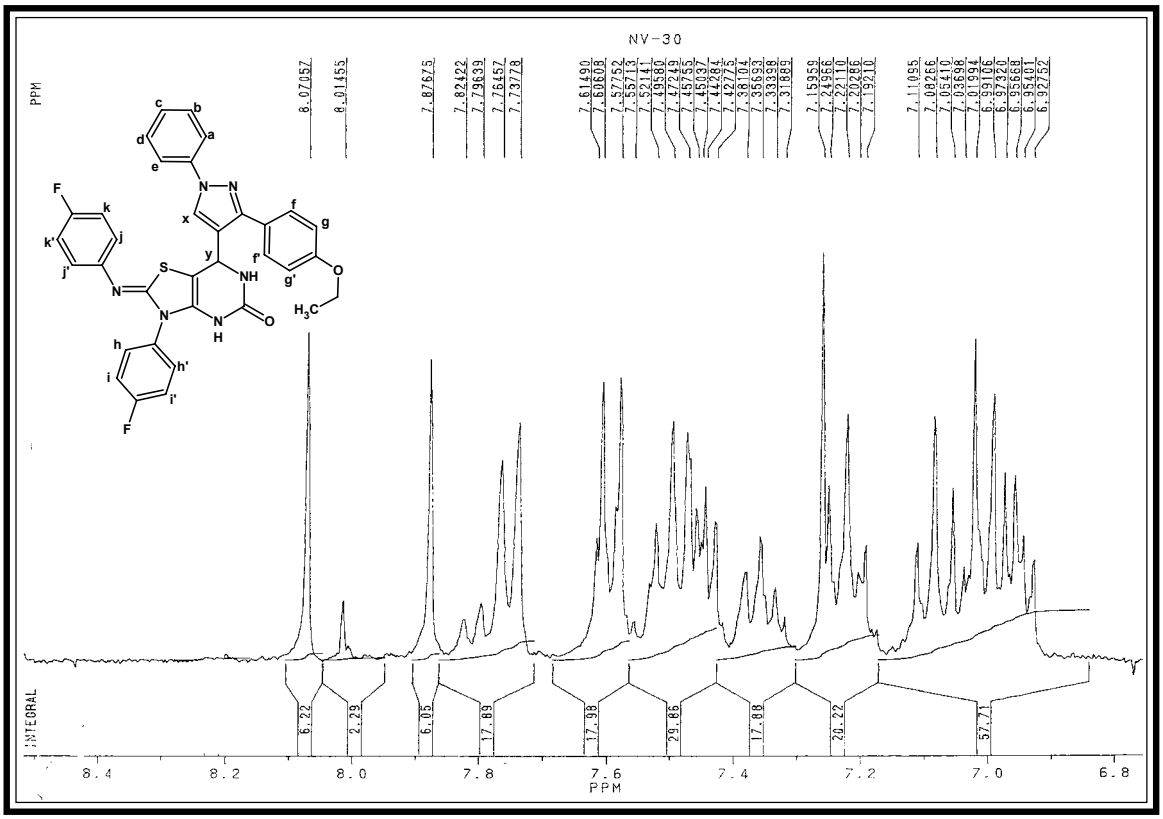
PMR SPECTRAL STUDY OF 6-*p*-FLUOROPHENYLIMINO-7,N-*p*-FLUOROPHENYL-2-OXO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.25-1.47	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.81
2.	4.08-4.11	2H	quartret	$-O\underline{CH}_2CH_3$	J_{CH_2}=6.92
3.	6.95-6.97	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.7
4.	6.99-6.01	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.6
5.	7.05-7.08	2H	doublet	Ar-$H_{jj'}$	J_{jk}=8.5
6.	7.22-7.24	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.5
7.	7.33-7.38	2H	triplet	Ar-H_{bd}	-
8.	7.42-7.52	3H	multiplet	Ar-$H_{a,c,e}$	-
9.	7.57-7.60	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.5
10.	7.76-7.73	2H	doublet	Ar-$H_{kk'}$	J_{kj}=8.7
11.	7.87	1H	singlet	CH_y	-
12.	8.07	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION

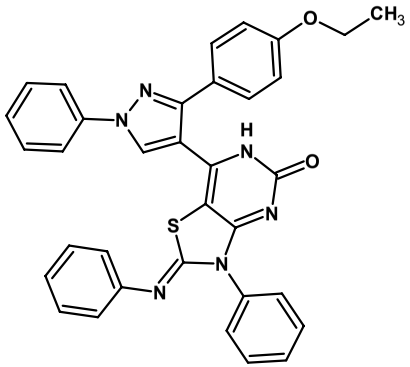


IR SPECTRAL STUDY OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES

Sr. No.	R	C=O str.
5a	C_6H_5-	1708
5b	4-OCH_3-C_6H_4-	1712
5c	3-OCH_3-C_6H_4-	1710
5d	4-CH_3-C_6H_4-	1706
5e	3-CH_3-C_6H_4-	1714
5f	4-OH-C_6H_4-	1705
4g	4-F-C_6H_4-	1708
5h	4-Cl-C_6H_4-	1710
5i	4-Br-C_6H_4-	1715
5j	3,4-$(Cl)_2$-C_6H_3-	1712
5k	4-NO_2-C_6H_4-	1710
5l	3-NO_2-C_6H_4-	1712

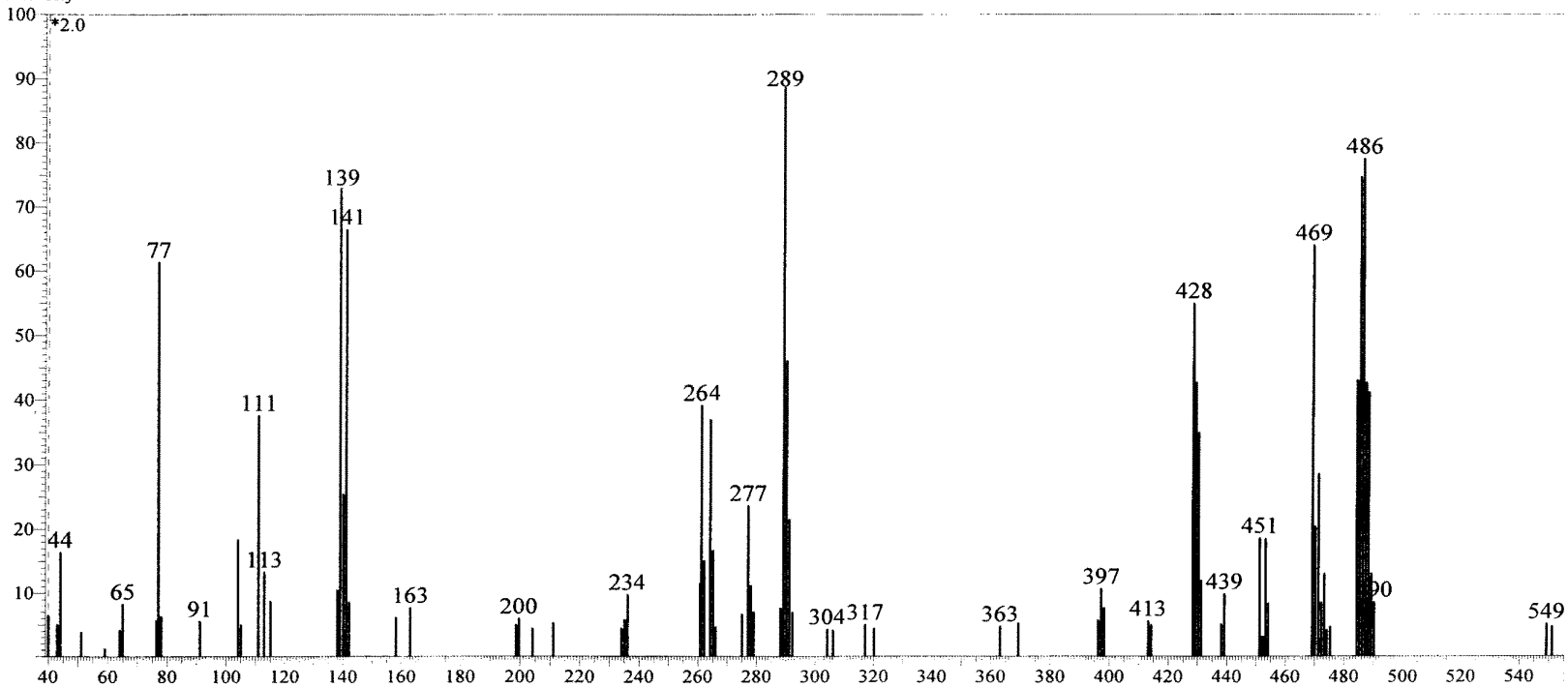
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information



Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/13/2005 12:16:53 PM
Sample Name : NV-9
Sample ID : NV-9
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-9.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune8.qgt

Line#:1 R.Time:14.3(Scan#:1677)
MassPeaks: 228 BasePeak 289 50705)
RawMode:Single 14.3(1677)
BG Mode:None
intensity



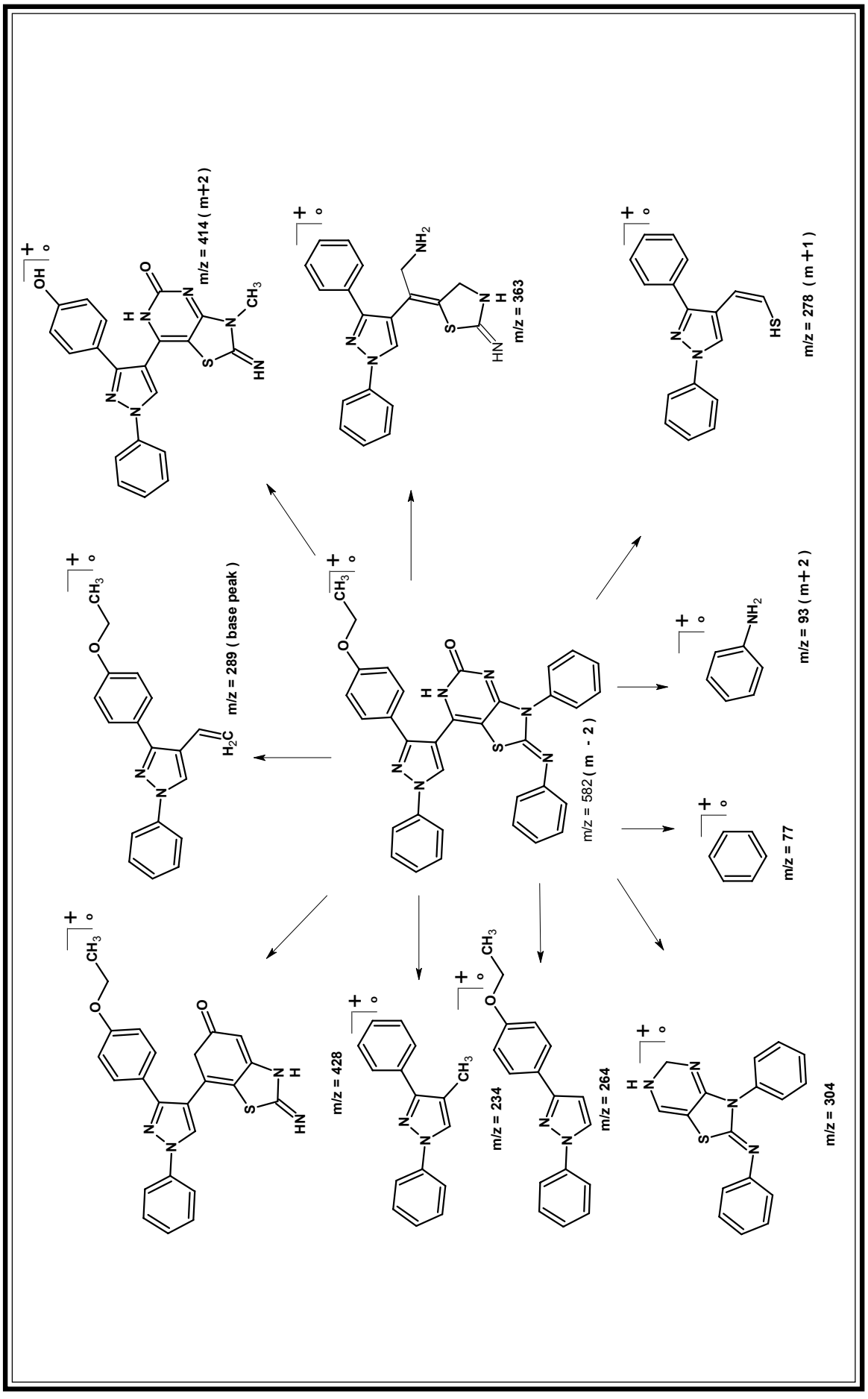
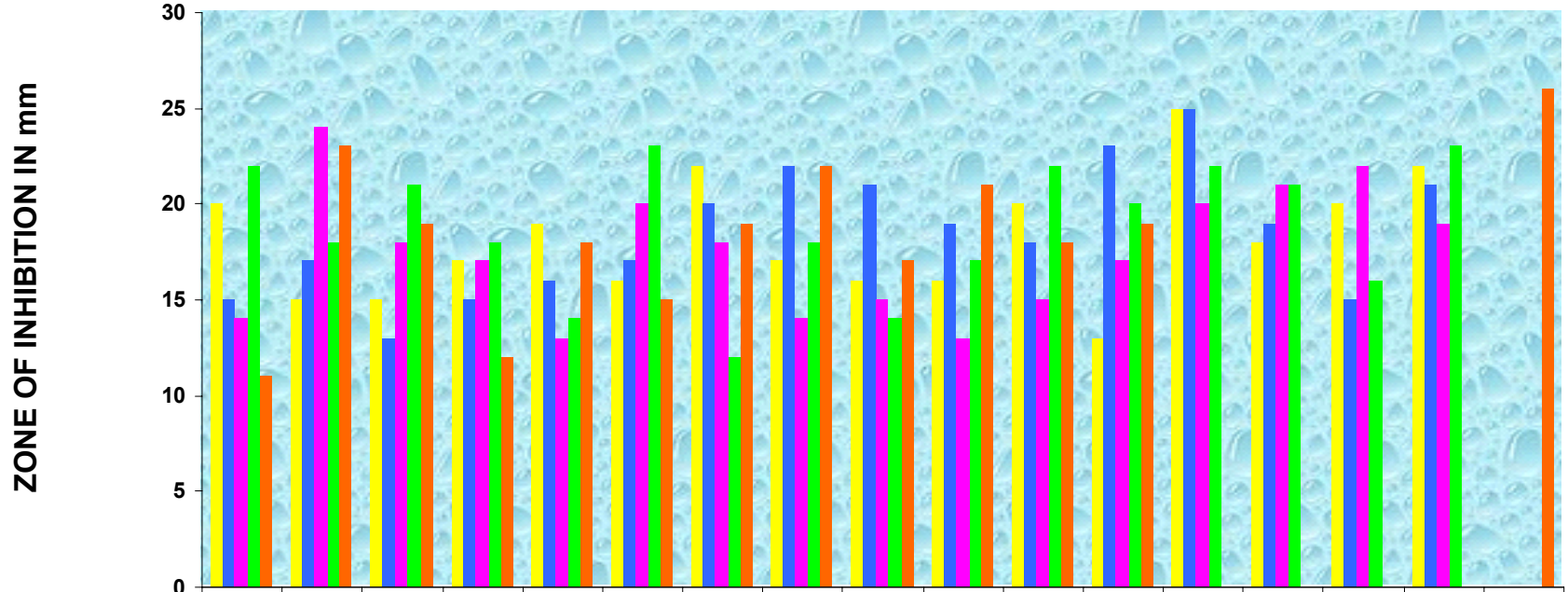

m/z = 582 (m - 2)
m/z = 414 (m+2)
m/z = 363
m/z = 278 (m +1)
m/z = 289 (base peak)
m/z = 93 (m+ 2)
m/z = 77
m/z = 428
m/z = 234
m/z = 264
m/z = 304

TABLE-5 : PHYSICAL CONSTANTS OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
5a	C_6H_5-	$C_{34}H_{28}N_6O_2S$	584	125	0.58	66	14.37	14.32
5b	4-OCH_3-C_6H_4-	$C_{36}H_{32}N_6O_4S$	644	144	0.66	61	13.03	12.98
5c	3-OCH_3-C_6H_4-	$C_{36}H_{32}N_6O_4S$	644	235	0.67	62	13.03	12.97
5d	4-CH_3-C_6H_4-	$C_{36}H_{32}N_6O_2S$	612	145	0.71	71	13.72	13.68
5e	3-CH_3-C_6H_4-	$C_{36}H_{32}N_6O_2S$	612	202	0.64	54	13.72	13.68
5f	4-OH-C_6H_4-	$C_{34}H_{28}N_6O_4S$	616	105	0.50	69	13.63	13.58
5g	4-F-C_6H_4-	$C_{34}H_{26}F_2N_6O_2S$	620	232	0.57	72	13.54	13.48
5h	4-Cl-C_6H_4-	$C_{34}H_{26}Cl_2N_6O_2S$	653	136	0.62	59	12.86	12.80
5i	4-Br-C_6H_4-	$C_{34}H_{26}Br_2N_6O_2S$	742	149	0.64	54	11.32	11.27
5j	3,4-$(Cl)_2$-C_6H_3-	$C_{34}H_{24}Cl_4N_6O_2S$	722	185	0.56	61	11.63	11.28
5k	4-NO_2-C_6H_4-	$C_{34}H_{26}N_8O_6S$	674	210	0.55	67	16.61	16.57
5l	3-NO_2-C_6H_4-	$C_{34}H_{26}N_8O_6S$	674	269	0.57	76	16.61	16.58

*TLC Solvent System :Ethylacetate : Hexane (1.8 : 8.2)

GRAPHICAL CHART NO. 5 : ANTIMICROBIAL ACTIVITY OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	20	15	15	17	19	16	22	17	16	16	20	13	25	18	20	22	0
S. aureus	15	17	13	15	16	17	20	22	21	19	18	23	25	19	15	21	0
E. aerogenes	14	24	18	17	13	20	18	14	15	13	15	17	20	21	22	19	0
P. aeruginosa	22	18	21	18	14	23	12	18	14	17	22	20	22	21	16	23	0
A. niger	11	23	19	12	18	15	19	22	17	21	18	19	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been concluded from the experimental data that the compounds bearing R= 4-fluorophenyl have displayed good activity against ***B.coccus***. The compounds bearing R= 4-chlorophenyl, 4-bromophenyl and 3-nitrophenyl have show considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains all the compounds were inactive against ***E.aerogenes*** except the compound bearing R=4-anisyl. While the compounds bearing R=phenyl, 3-anisyl,4-hydroxyphenyl and 4-nitrophenyl showed significant activity against ***P.aeruginosa***.

ANTIFUNGAL ACTIVITY

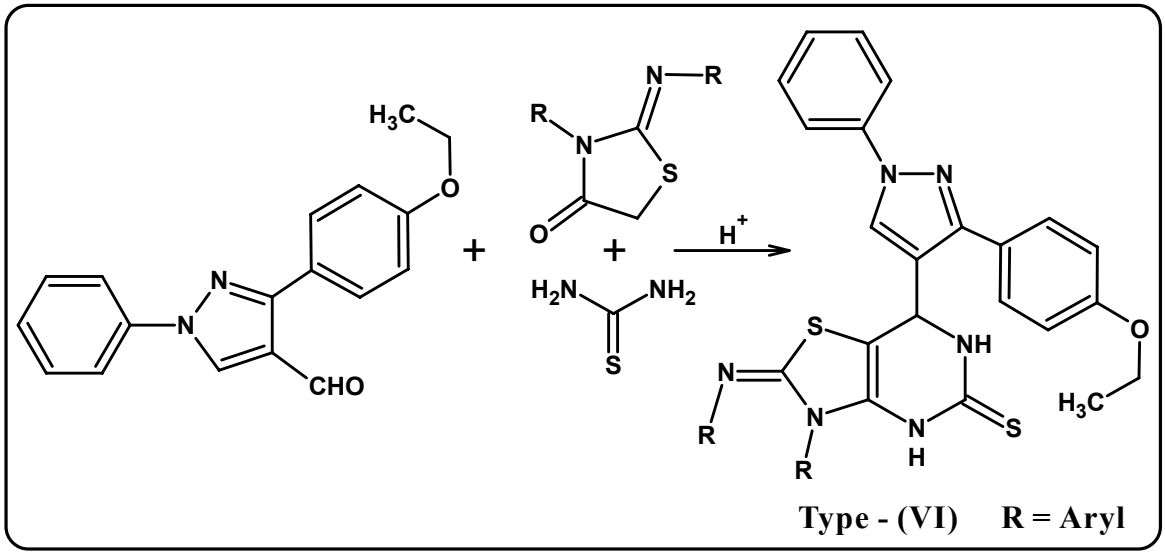
All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=4-anisyl,3,4-dichlorophenyl and 4-chlorophenyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drug viz.amoxicillin,benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

SECTION - III

SYNTHESIS AND THERAPEUTIC EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES

In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. It was considered worthwhile to synthesise thiopyrimidines of type (VI), which have been prepared by the condensation of 2-arylimino-3-aryl-5H-4-thiazolidinone, 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl-pyrazole and thiourea in glacial acetic acid with fused sodium acetate.



Type - (VI) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDRO-THIAZOLIDINO-[4,5-e]-PYRIMIDINES

[A] Preparation of 2-*p*-Fluorophenylimino-3-(*p*-fluorophenyl)-5H-4-thiazolidinone[157]

See, Part-II, Section-I (B)

[B] Preparation of 6-(*p*-Fluorophenylimino)-7,N-(*p*-fluoropheny)-2-thio-4-(1',N-phenyl-3'-(*p*-ethoxyphenyl-pyrazol-4'-yl)-1,2,3,4tetrahydro thiazolidino-[4,5-e]-pyrimidine

A mixture of 2-*p*-fluorophenylimino-3-(*p*-fluorophenyl)-5H-4-thiazolidinone (3.36g, 0.01M) 1,N-phenyl-3-(2',4'-dichlorophenyl)-4-formyl-pyrazole (2.92g, 0.01M) and thiourea (0.76g, 0.01M) were mixed in glacial acetic acid (20 ml) with fused sodium acetate(1.25g, 0.015M). The reaction mixture was refluxed for 12 hrs. cooled and poured into crushed ice. The product was isolated and crystallised from methanol-DMF. Yield 52%, m.p. 148^{o}C ($C_{34}H_{26}F_2N_6OS_2$, Found : C, 64.13`%; H, 4.12%; N, 13.24% Requires : C, 64.08%; H, 4.08%; N, 13.20%;).

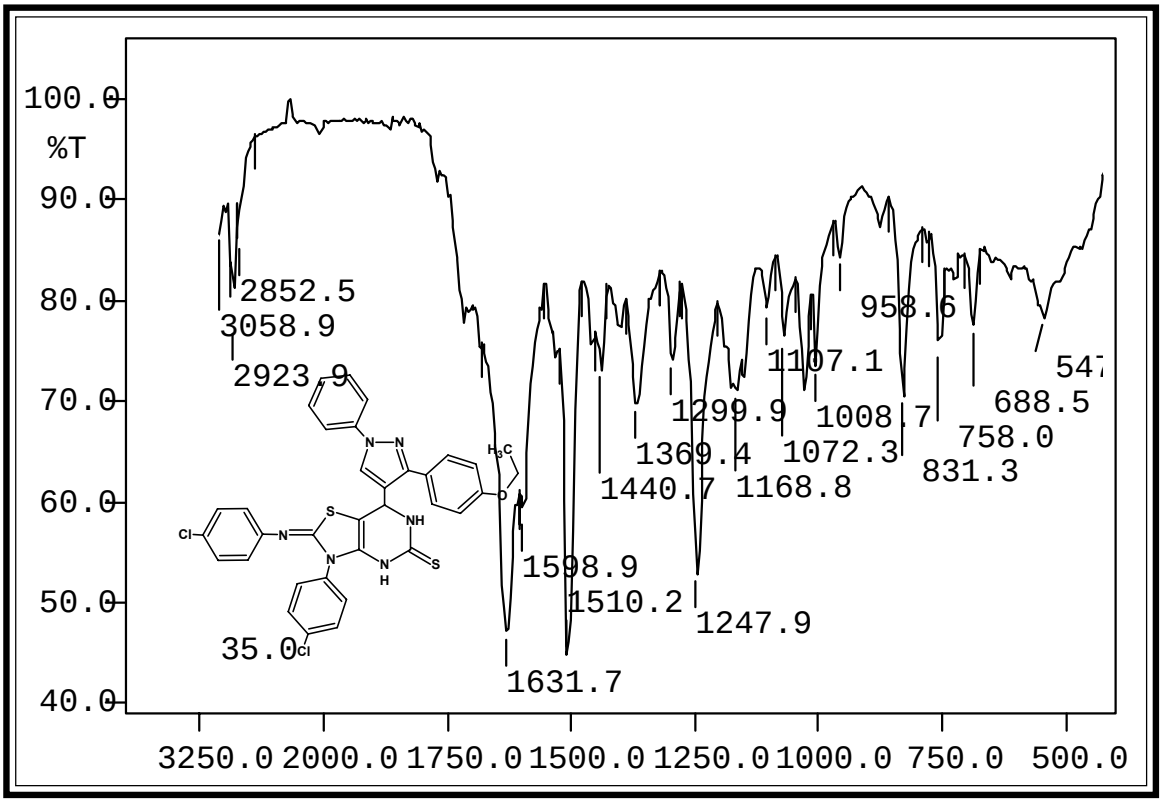
TLC solvent system : Acetone : Benzene (2.5 : 7.5).

Similarly other pyrimidines were prepared. The physical data are recorded in Table No. 6.

[C] Therapeutical activity of 6-Arylimino-7,N-aryl-2-thio-4-[1',N-phenyl-3'-(*p*-ethoxyphenyl)-pyrazol-4'-yl]-1,2,3,4-tetrahydro-thiazolidino-(4,5-e)-pyrimidines

Antimicrobial testing was carried out as described in [A] Part-I, Section-I(D). The zone of inhibition of the test solution are recorded in Graphical Chart No.6.

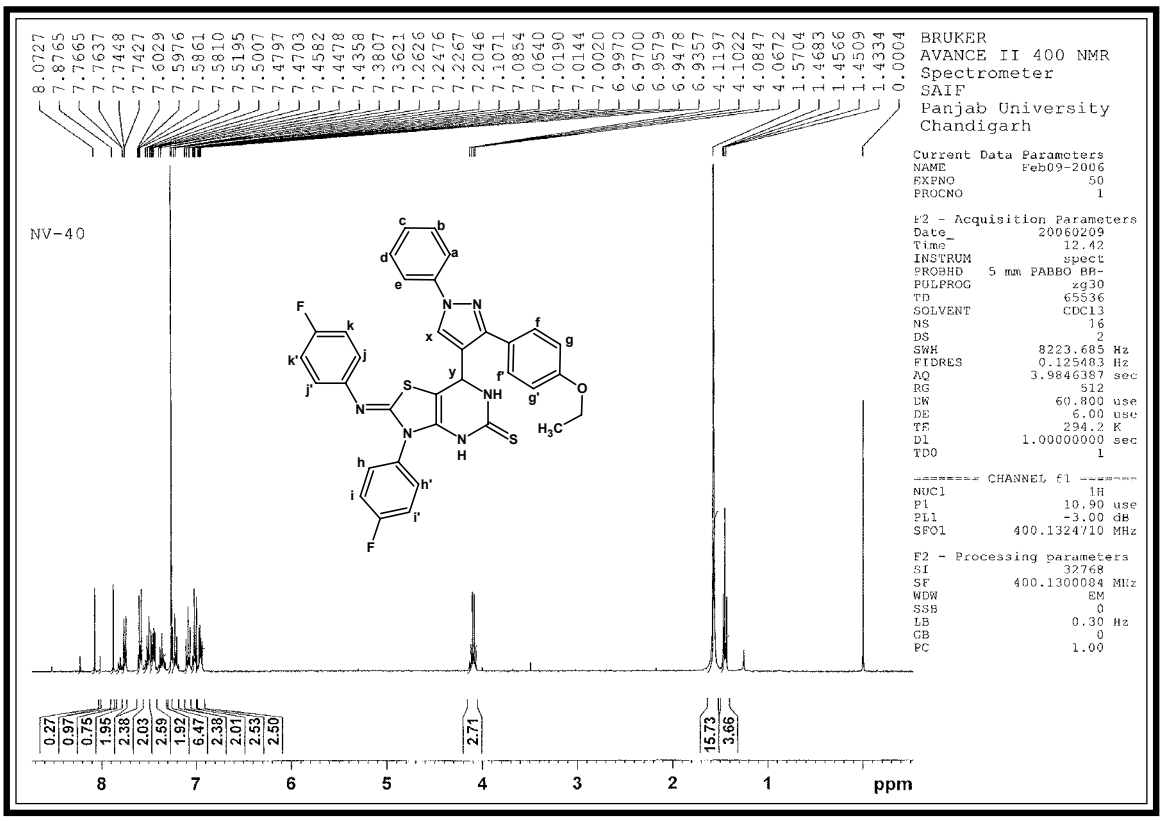
IR SPECTRAL STUDY OF 6-*p*-CHLOROPHENYLIMINO-7,N-*p*-CHLOROPHENYL-2-THIO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	413
-CH_3	C-H str. (sym.)	2852	2880-2860	
	C-H i.p.def. (asym.)	1440	1470-1435	
Aromatic	C-H str.	3058	3080-3030	
	C=C str.	1598	1585-1480	414
	C-H i.p. def.	1107	1125-1090	
	C-H o.o.p. def	831	835-810	
Pyrazole	C=N str.	1631	1630-1590	415
moiety	C-N str.	1168	1230-1020	
	C-Cl str.	688	800-600	413
	C-S-C str. (sym.)	1026	1075-1020	
Pyrimidine	N-H str.	3435	3500-3350	416
ring	C=N str.	1631 (overlapped)	1650-1550	
	C=S str.	750	700-750	

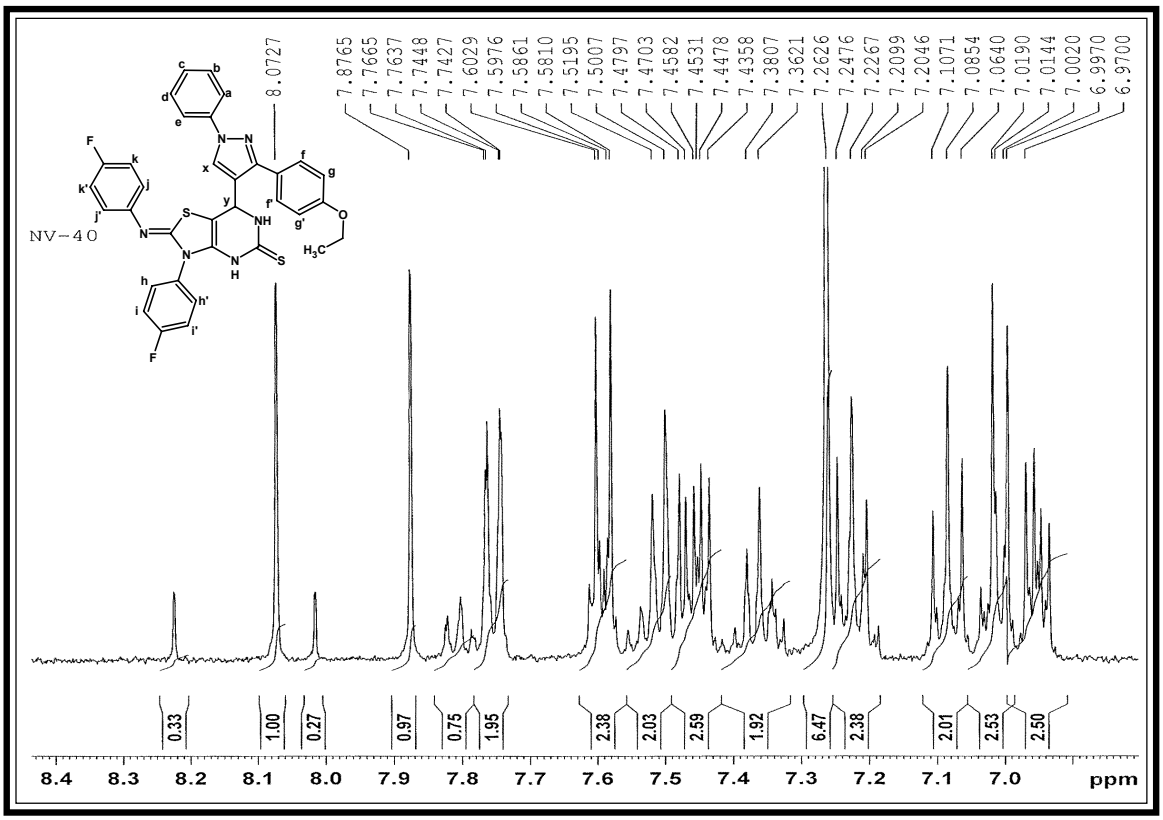
PMR SPECTRAL STUDY OF 6-*p*-FLUOROPHENYLIMINO-7,N-*p*-FLUOROPHENYL-2-THIO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE

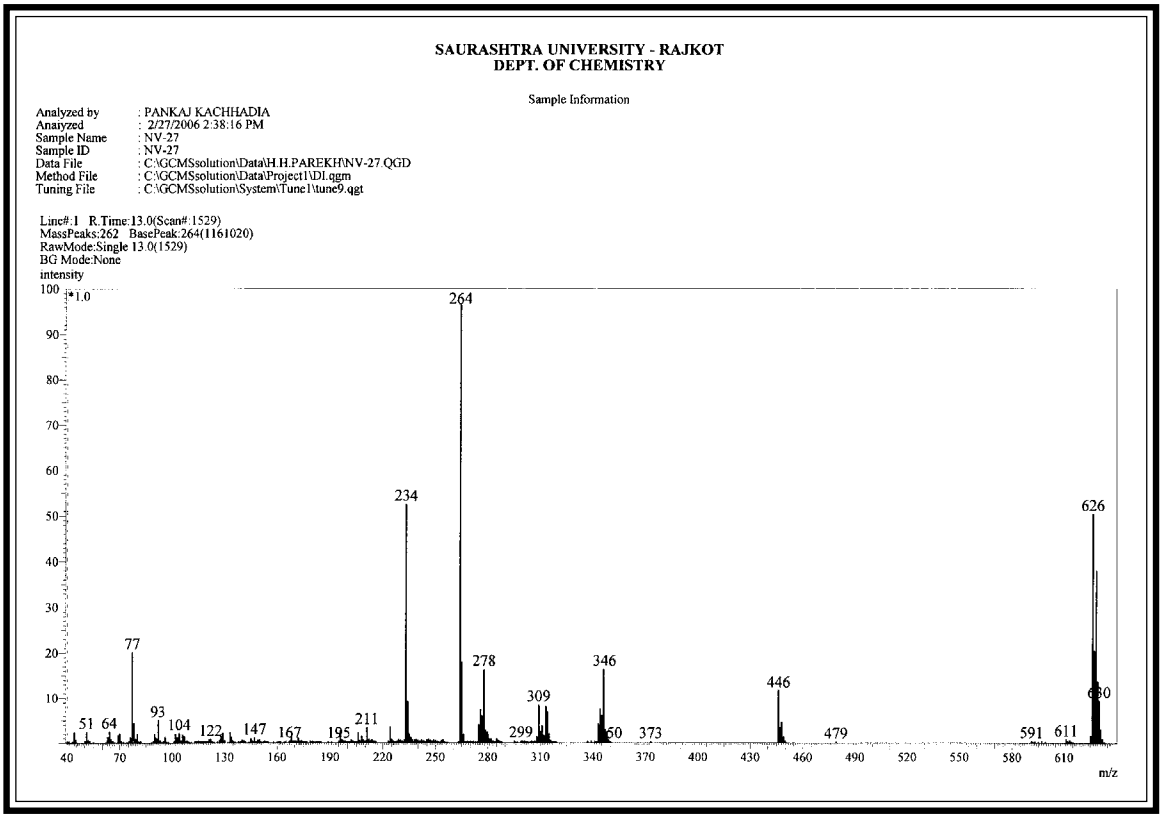


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.43-1.46	3H	triplet	-$OCH_2\underline{CH}_3$	J_{CH_3}=6.81
2.	4.06-4.11	2H	quartret	-$O\underline{CH}_2CH_3$	J_{CH_2}=6.92
3.	6.93-6.97	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.4
4.	6.99-7.01	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.4
5.	7.06-7.10	2H	doublet	Ar-$H_{jj'}$	J_{jk}=8.6
6.	7.22-7.24	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.3
7.	7.36-7.38	1H	triplet	Ar-H_c	-
8.	7.44-7.51	4H	multiplet	Ar-$H_{a,b,d,e}$	-
9.	7.58-7.60	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.4
10.	7.74-7.76	2H	doublet	Ar-$H_{kk'}$	J_{kj}=8.6
11.	7.87	1H	singlet	CH_y	-
12.	8.07	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION





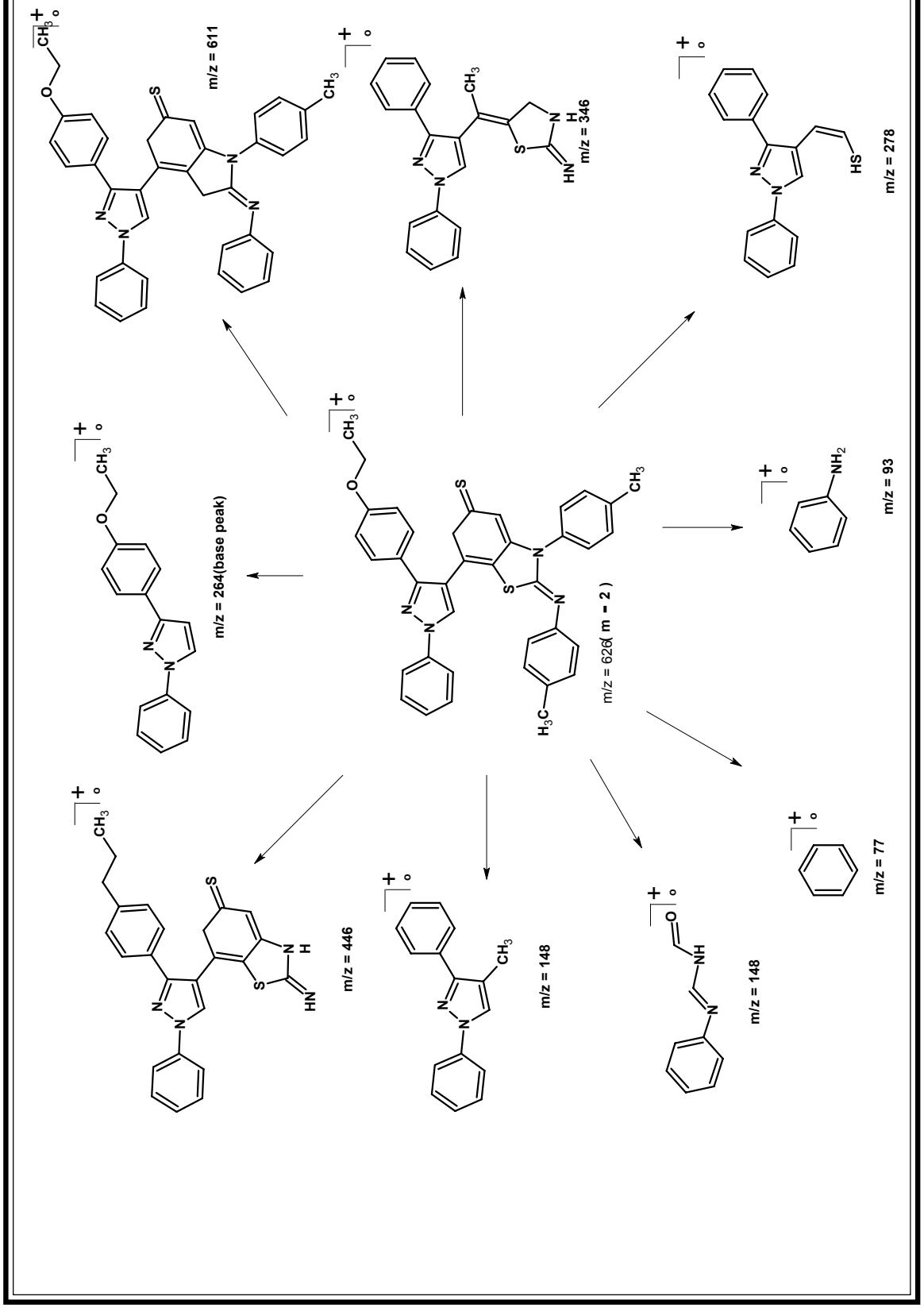
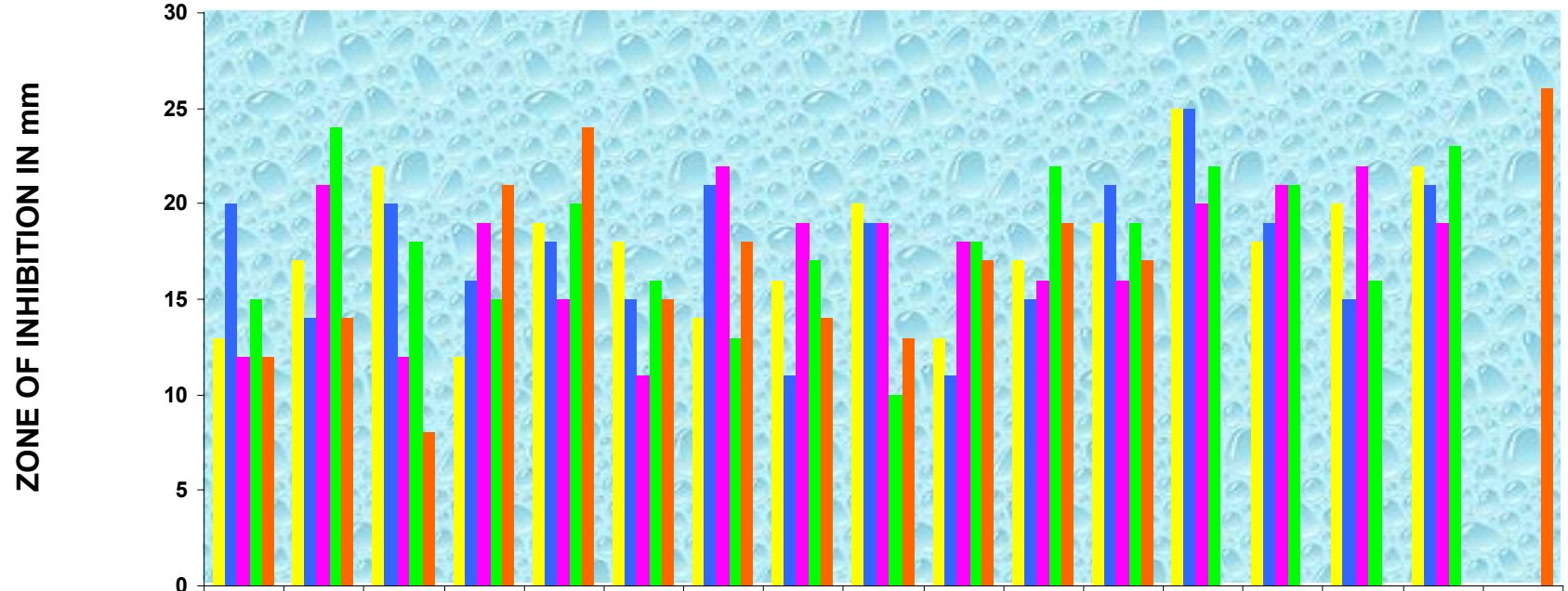

m/z = 611
m/z = 346
m/z = 278
m/z = 264(base peak)
m/z = 626(m - 2)
m/z = 93
m/z = 446
m/z = 148
m/z = 148
m/z = 77

TABLE-6 : PHYSICAL CONSTANTS OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
6a	C_6H_5-	$C_{34}H_{28}N_6OS_2$	600	169	0.59	71	14.64	14.59
6b	4-OCH_3-C_6H_4-	$C_{36}H_{32}N_6O_3S_2$	660	159	0.59	69	12.76	12.69
6c	3-OCH_3-C_6H_4-	$C_{36}H_{32}N_6O_3S_2$	660	148	0.57	58	12.76	12.71
6d	4-CH_3-C_6H_4-	$C_{36}H_{32}N_6OS_2$	628	215	0.68	69	13.41	13.35
6e	3-CH_3-C_6H_4-	$C_{36}H_{32}N_6OS_2$	628	108	0.64	58	13.41	13.36
6f	4-OH-C_6H_4-	$C_{34}H_{28}N_6O_3S_2$	632	268	0.50	70	13.32	13.27
6g	4-F-C_6H_4-	$C_{34}H_{26}F_2N_6OS_2$	636	148	0.57	52	13.24	13.20
6h	4-Cl-C_6H_4-	$C_{34}H_{26}Cl_2N_6OS_2$	669	198	0.62	63	12.59	12.53
6i	4-Br-C_6H_4-	$C_{34}H_{26}Br_2N_6OS_2$	758	128	0.67	58	11.11	11.09
6j	3,4-$(Cl)_2$-C_6H_3-	$C_{34}H_{24}Cl_4N_6OS_2$	738	176	0.56	69	11.41	11.38
6k	4-NO_2-C_6H_4-	$C_{34}H_{26}N_8O_5S_2$	690	164	0.59	71	16.27	16.19
6l	3-NO_2-C_6H_4-	$C_{34}H_{26}N_8O_5S_2$	690	228	0.60	52	16.27	16.18

*TLC Solvent System : Acetone : Benzene (2.5 : 7.5)

GRAPHICAL CHART NO. 6 : ANTIMICROBIAL ACTIVITY OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-(p-ETHOXYPHENYL) PYRAZOL-4'-YL],1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-e]-PYRIMIDINES



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Greseofulvin
B. coccus	13	17	22	12	19	18	14	16	20	13	17	19	25	18	20	22	0
S. aureus	20	14	20	16	18	15	21	11	19	11	15	21	25	19	15	21	0
E. aerogenes	12	21	12	19	15	11	22	19	19	18	16	16	20	21	22	19	0
P. aeruginosa	15	24	18	15	20	16	13	17	10	18	22	19	22	21	16	23	0
A. niger	12	14	8	21	24	15	18	14	13	17	19	17	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

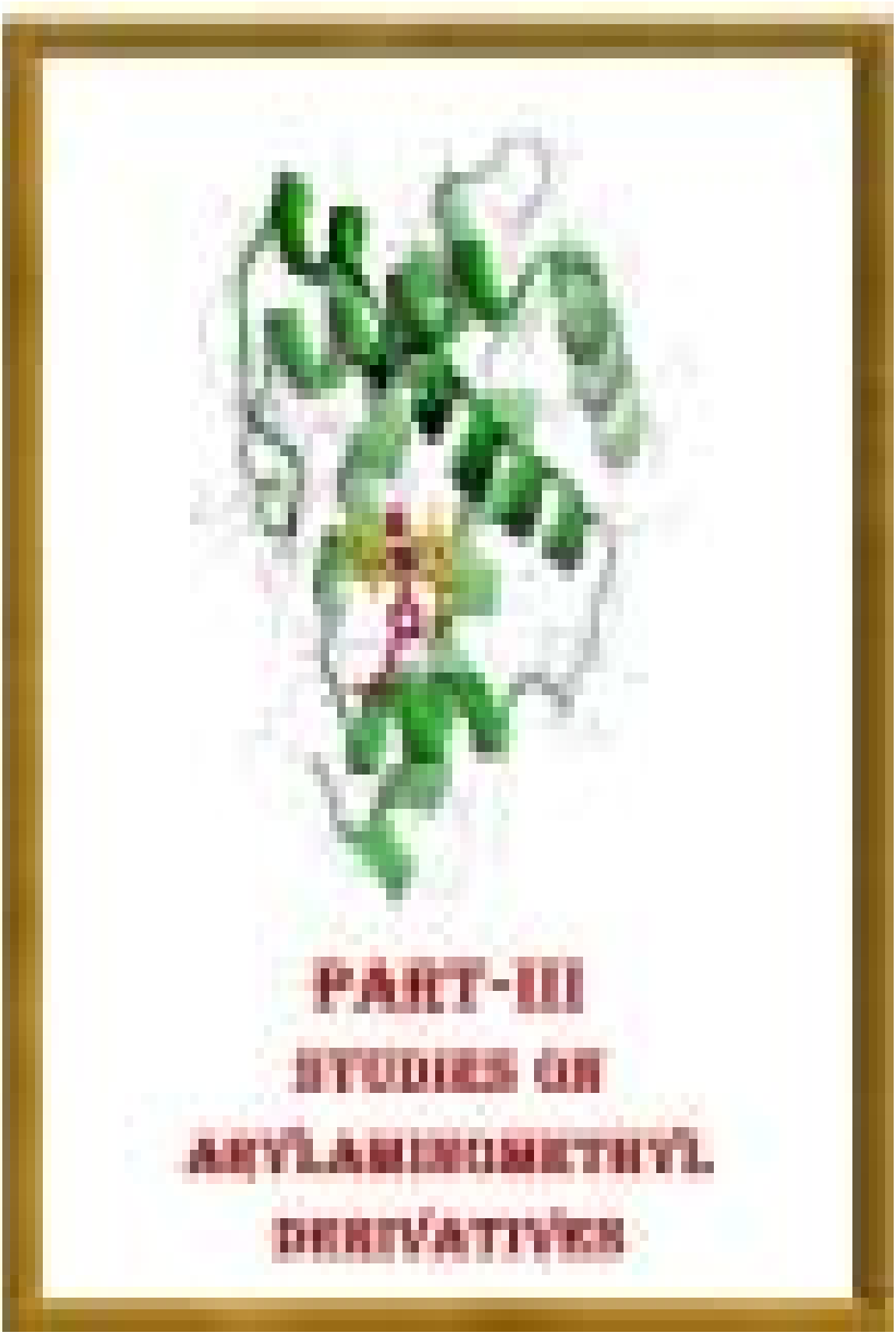
It has been concluded from the experimental data that the compounds bearing R=3-anisyl have displayed good activity against ***B.coccus***. The compounds bearing R= 4-fluorophenyl and 3-nitrophenyl have shown considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains, all the compounds were inactive against ***E.aerogenes*** except the compound bearing R=4-anisyl and 4-fluorophenyl. While the compounds bearing R=4-anisyl and 4-nitrophenyl showed significant activity against ***P.aeruginosa***.

ANTIFUNGAL ACTIVITY

All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=4-tolyl and 3-tolyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drug viz.amoxicillin,benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.



PART-III

STUDIES ON ARYLAMINOMETHYL DERIVATIVES

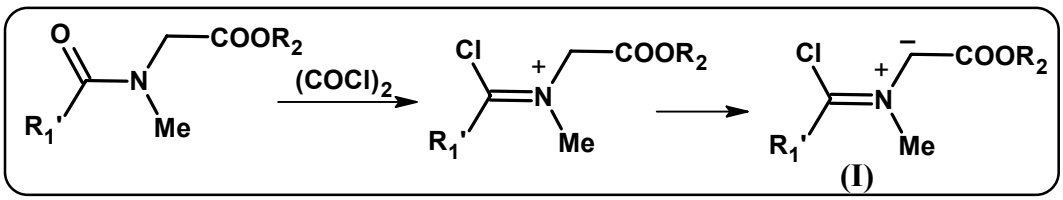
INTRODUCTION

Azomethine derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activities.Azomethines are also known as Schiff bases and they are well known intermediate for the preparation of azetidinones, thiazolidinones ,formazan,aryl acetamide and many other entities of pharmaceutical potential. These are the compounds containing characteristic -HC=N- group

Azomethines are imino compounds which are formed by the reaction of primary amine with aldehydes or ketones.When one or both of reactants is aromatic, the imine is stable. In case of aliphatic reactants the imines tend to decompose or polymerized.

SYNTHETIC ASPECTS

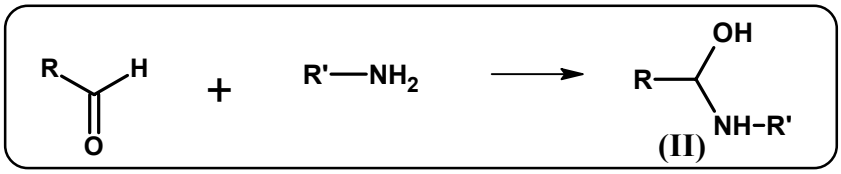
1. Recently , Rosallen J Anderson et al.[158] have discovered new method for synthesis of azomethine derivatives with the use of chlorominium salt.



(I)

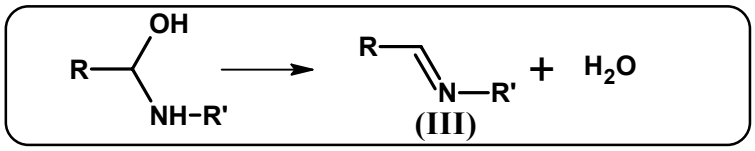
2 . Imine formation involves two steps.[159]

(a) Addition of the amine to the carbonyl group of the aldehyde yields aldol .The aldol is rarely capable of isolation.



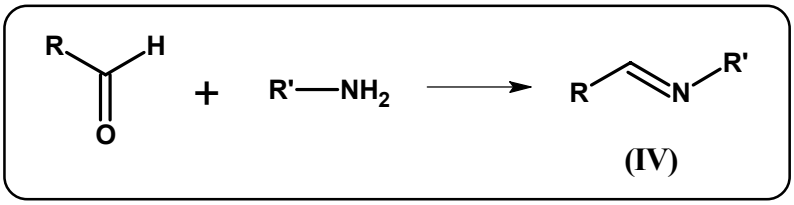
(II)

(b) The loss of water to give an imine (azomethine). This corresponds to the "crotonaldehyde stage" of the aldol condensation.



(III)

3. Schiff base have been synthesised by the reaction of aldehyde with amine.[160]



(IV)

THERAPEUTIC IMPORTANCE

Azomethine derivatives are excellent bioactive substances in pharmaceutical industry. Inthe past years, the literature is enriched with progressive findings about the synthesis and pharmacological action of azomethine derivatives. The important activities are as under.

(a) Antifungal[161]

(b) Antiinflammatory[162]

(c) Antibacterial[163]

(d) Antischistosomal[164]

(e) Antiparasitic[165]

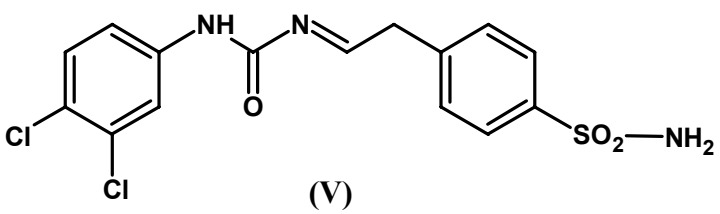
(f) Plant hormone activity[166]

(g) Antiviral[167]

(h) Antipyratic[168]

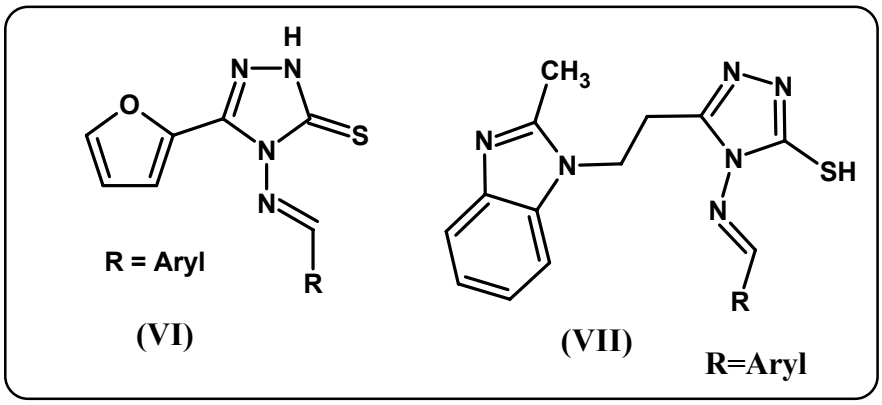
(i) Herbicidal[169]

Jerpan Krungkrai and co-workers[170] have synthesised azomethine derivatives(V) which showes antimalarial actvity. The malarial parasite *Plasmodium falciparum* encodes for an a-cabonic anhydrase (CA) enzyme possessing catalytic properties distinct of that of the human host and the synthesised compounds inhibiting a critical enzyme for the life cycle of the parasite.



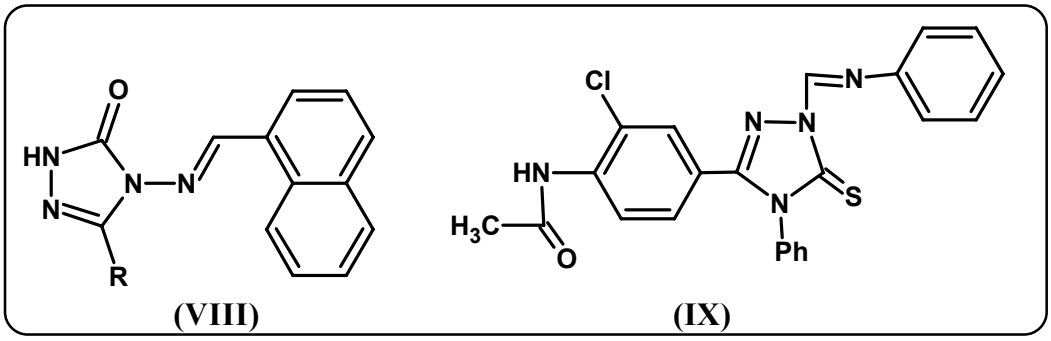
(V)

Popesal et.al.[171] suggested some schiff bases useful as carbonic anhydrase inhibitors. Ergenc et.al.[172] have synthesised azomethine derivatives (VI) showing antifungal activity.



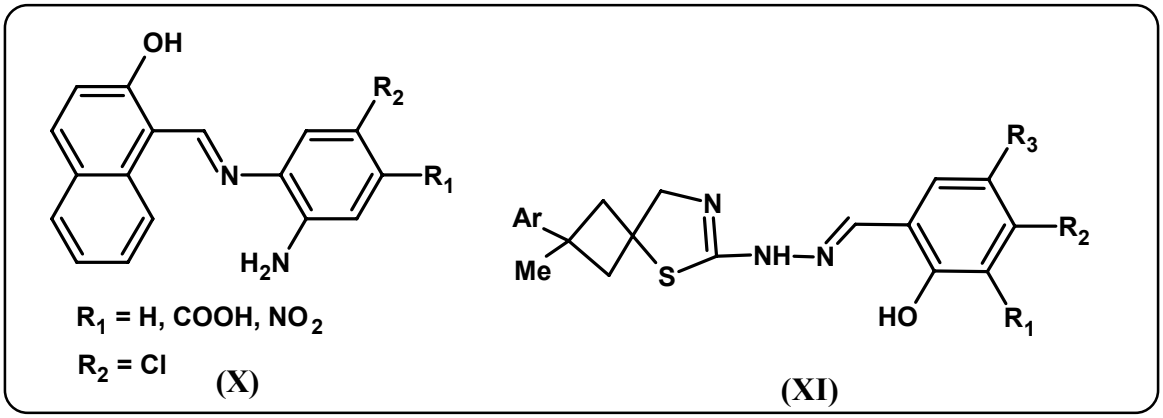
Afaf H .and co-workers[173] have prepared azomethines (VII) possessing potential antimicrobial activity. Wang Y. et al.[174] have screened azomethines having good plant hormone activity. Nadine Azas et al.[175] have documented azomethine derivative and screened for their antiparasitic activity against *plasmodium falciparum*, *Trichomonas faginalis* and compared their toxicity versus human cell. Jayendra Patole et al.[176] have prepared some Schiff bases and evaluated them as antitubercular agent.

J.M. Monti et al.[177] have reported azomethines useful as H3-antaganist. S.Guniz Kucukguzel et al.[178] have screened azomethine derivatives for their anticonvulsant activity. Huseyin Unver et al.[179] have investigated azomethines and studied their antimicrobial activity. Neslihan and Reyhan[180] have synthesized a series of new azomethines (VIII) and tested them as antitumer agent. R.S.Varma[181] has synthesized a series of new azomethines (IX) and evaluated them for antileishmanial activity.



Christos A. et al.[182] have discovered several coumarin containing azomethine derivatives and tested *in vivo* for their anti-inflammatory activity and *in vitro* for their antioxidant ability. Ilkay Kucukguzel and co-workers[183] have synthesised Schiff bases of 4-alkyl/ aryl -5-(4- aminophenyl)-4H-1,2,4-triazoles and screened for their

anticonvulsant activity. Perumal Panneerseivamhave[184] discovered novel series of schiftf base of 4-(4-aminophenyl) morpholine and evaluated them as antimicrobial agent. Hojatollah M. et al.[185] have reported azomethines useful as anticonvulsant agent. Sham M.Sondhi et al.[186] have documented azomethine derivatives(X) & evaluated them for anti-inflammatory ,analgesic and kinase CDK-1, CDK-5, and GSK-3 inhibition activity.



Zhanyong Guo and co-workers[187] have discovered the azomethine derivatives and reported their antifungal and antioxident activity. Most of the compounds showed better inhibitory effect against *Fusarium oxyporium , Vasinfectum , Alternaria Solani and Valsa mali.* Alladdin et al.[188] have prepared schiff bases by combining 2,4 disubstituted thiazole and cyclobutane ring (XI) and studied their antibacterial properties against *C. tropicalis and Bacillus subtilis.*

Jayendra Patole et al.[189] reported novel schiff bases of *p*-aminosalicylic acid containing hydroxy rich side chains which enhanced antimycobacterial activity against *Mycobacterium Smegmatis* and Mycobacterium bovis BCG. Dharmarajan Shriram et al.[190] have synthesised azomethine derivatives and reported them as anti HIV agent.

In view of therapeutic activities of azomethines , it was contemplated to synthesise azomethine derivatives in search of agent possessing higher biological activity with least side effects , which have been described as under.

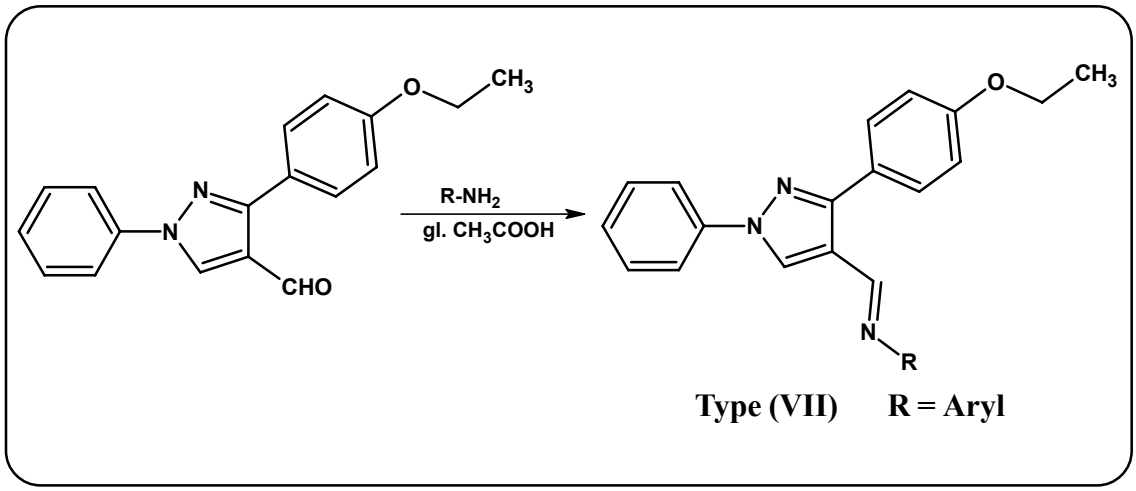
SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF N-ARYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-AZOMETHINES

SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ARYLAMINOMETHYL-1,N-PHENYL-3-(*p*- ETHOXYPHENYL) PYRAZOLES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF N-ARYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-YL-AZOMETHINES

Azomethine derivatives are well known for their pharmacological activities. Azomethines are also found as intermediate in organic synthesis. These findings encouraged us to synthesise some new azomethines of type (VII) bearing pyrazole nucleus. The synthesis was carried out by the condensation of 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl pyrazole wth different aromatic amines.

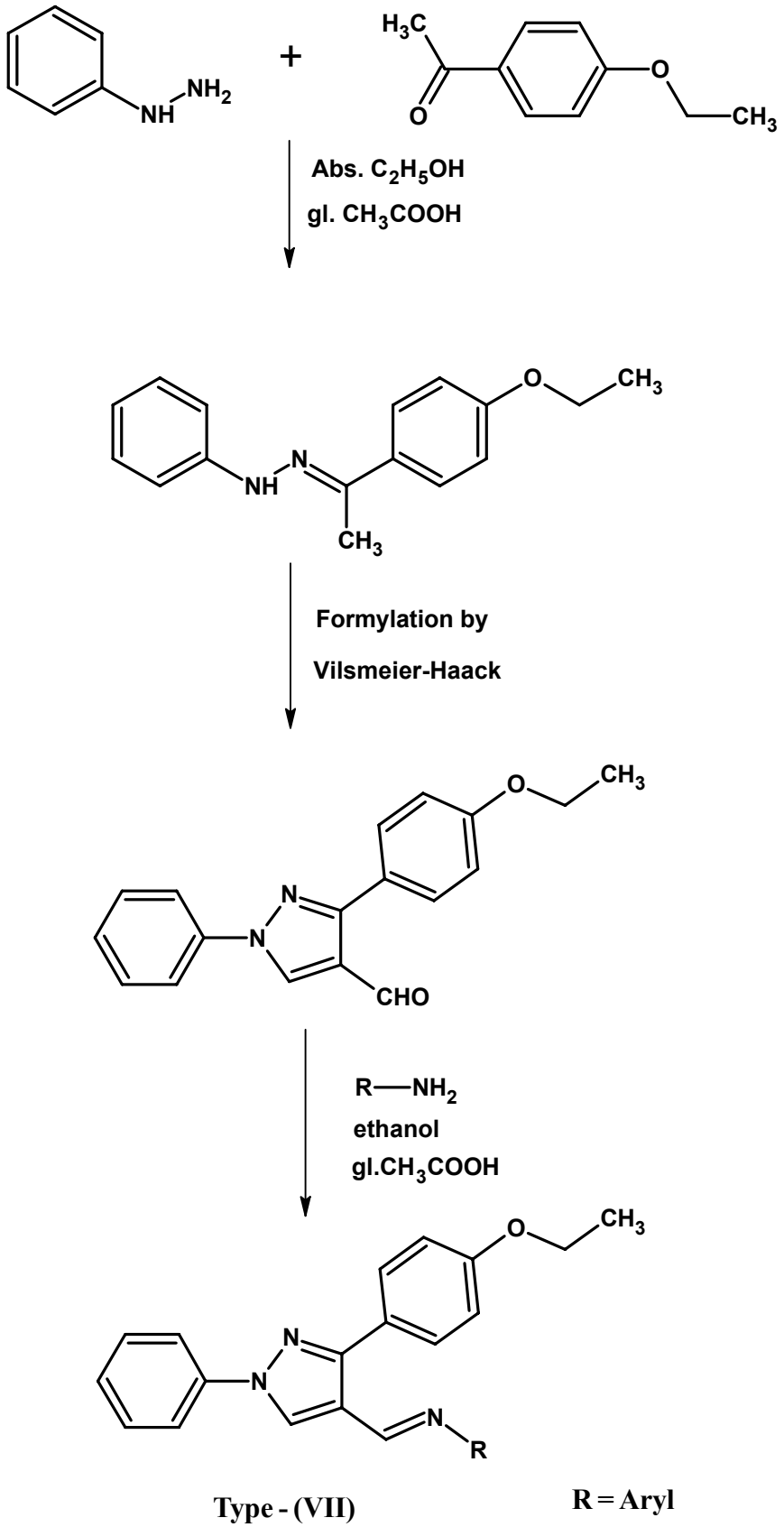


Type (VII) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (VII) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF N-ARYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-YL-AZOMETHINES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-(*p*-ethoxyphenyl)-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Preparation of N-(*p*-Chlorophenyl)-1,N-phenyl-3-(*p*-ethoxyphenyl)-pyrazol-4-yl-azomethines

A mixture of 1,N-phenyl-3-(*p*-ethoxyphenyl)-4-formyl pyrazole(2.92gm, 0.01M) and p-chloroaniline (1.27gm, 0.01M) was refluxed in ethanol (95%) for 10 hrs.with the use of gl CH_3COOH(1ml) as catalyst. The contents were cooled and product isolated was crystallised from ethanol. Yield 78%, m.p.160^{O}C, ($C_{24}H_{20}ClN_3O$; Found : C, 71.13; H, 5.02; N, 10.46 %; Required : C, 71.09%; H, 4.97 %; N, 10.40%).

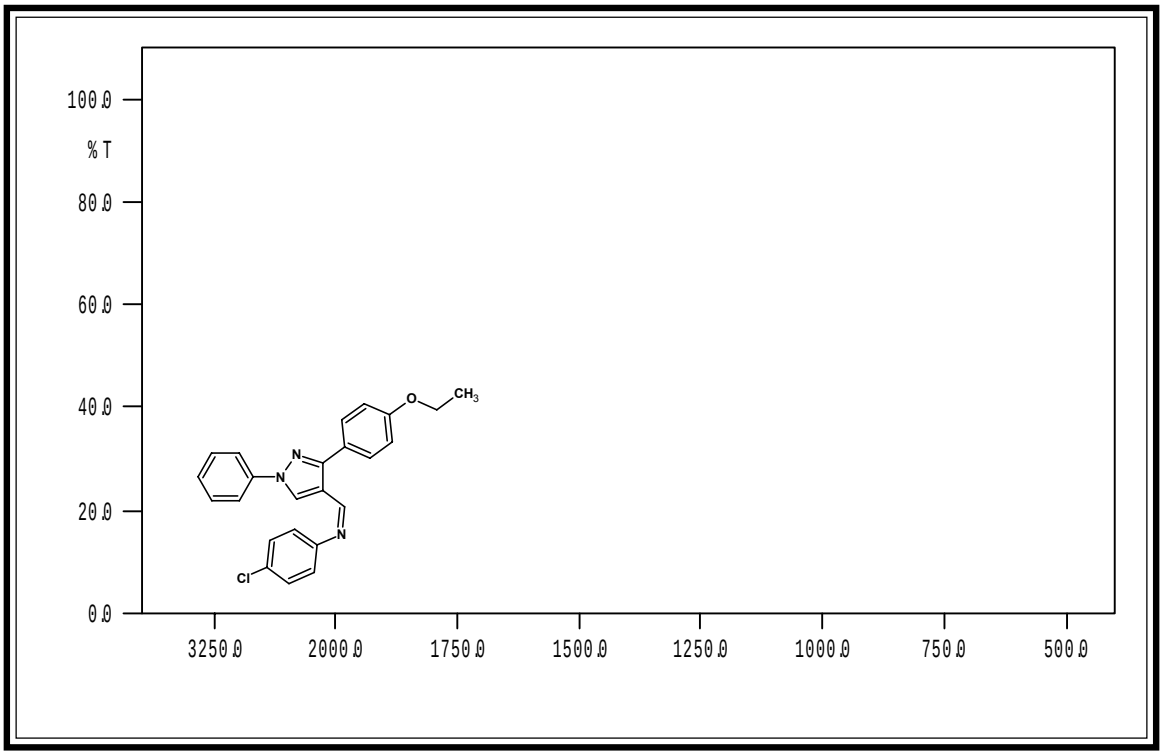
TLC solvent system : Ethyl acetate:Hexane (2.7:7.3).

Similarly other substituted azomethines have been prepared. The physical data are recorded in Table No. 7

(D) Antimicrobial activity of N-Aryl-1,N-phenyl-3-(*p*-ethoxyphenyl)-pyrazol-4-yl-azomethines

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 7.

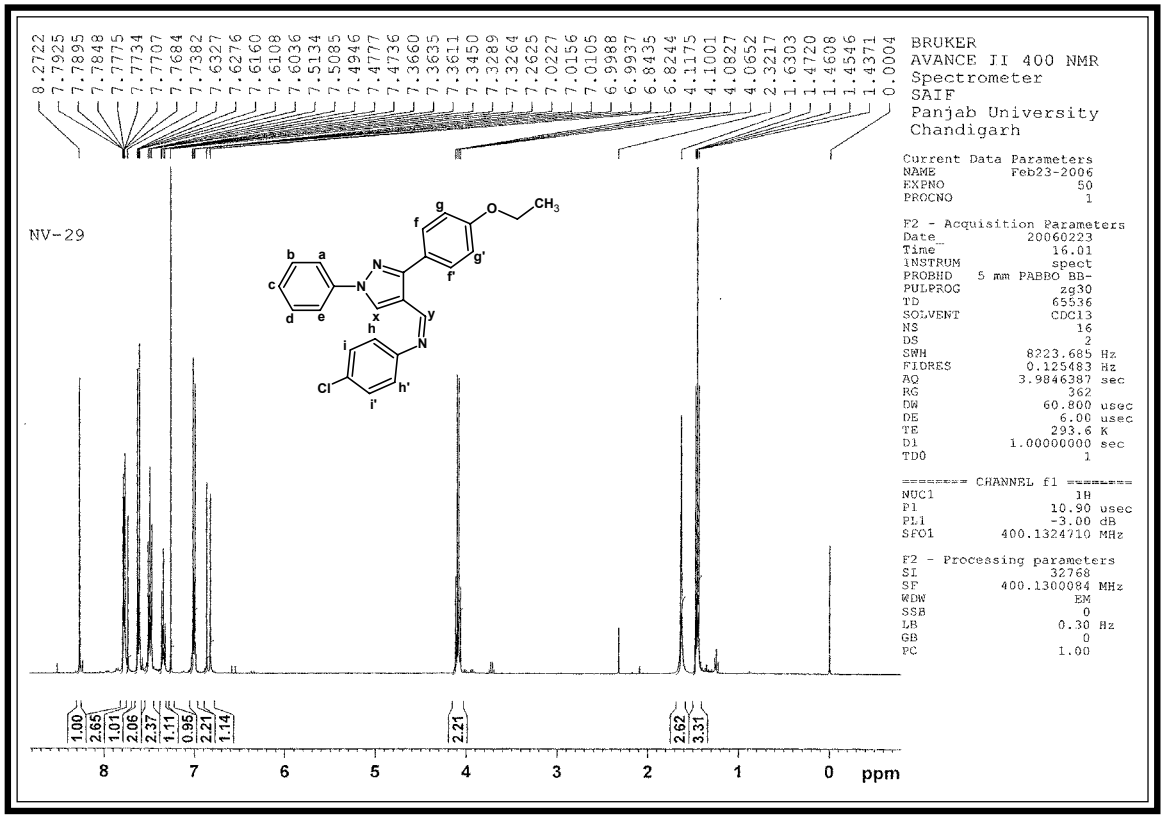
IR SPECTRAL STUDY OF N-(*p*-CHLOROPHENYL)-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-YL-AZOMETHINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	413
$-CH_3$	C-H str. (sym.)	2817	2880-2860	
	C-H i.p.def. (asym.)	1434	1470-1400	
	C-H o.o.p. def. (sym.)	1363	1390-1370	
Aromatic	C-H str.	3049	3080-3030	414
	C=C str.	1533	1585-1480	
	C-H i.p. def.	1101	1125-1090	
	C-H o.o.p. def	821	835-810	
Pyrazole	C=N str.	1583	1630-1590	415
moiety	C-N str.	1078	1230-1020	
	C-Cl str.	756	830-560	
Ether	C-O-C str. (asym.)	1232	1275-1200	413
	C-O-C str. (sym.)	1066	1075-1020	
Schiff Base	C=N str.	1645	1660-1580	415

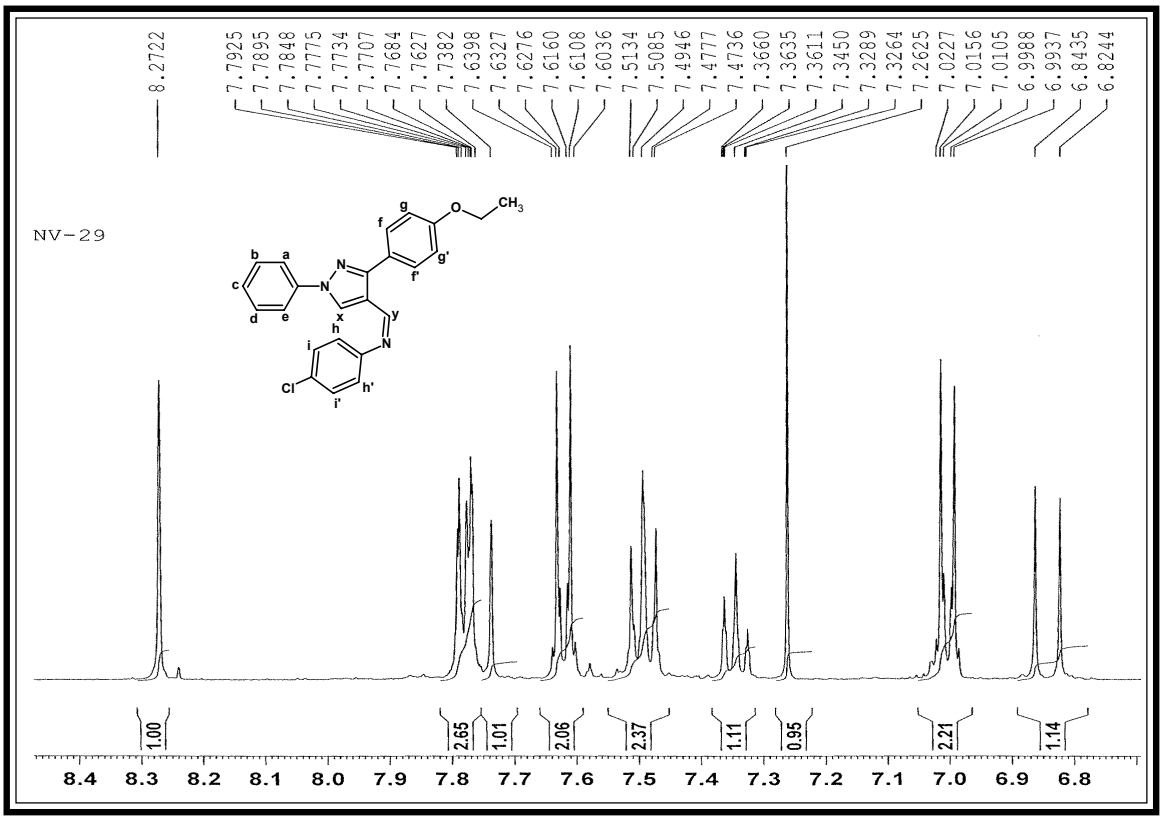
PMR SPECTRAL STUDY OF N-(*p*-CHLOROPHENYL)-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-YL-AZOMETHINE

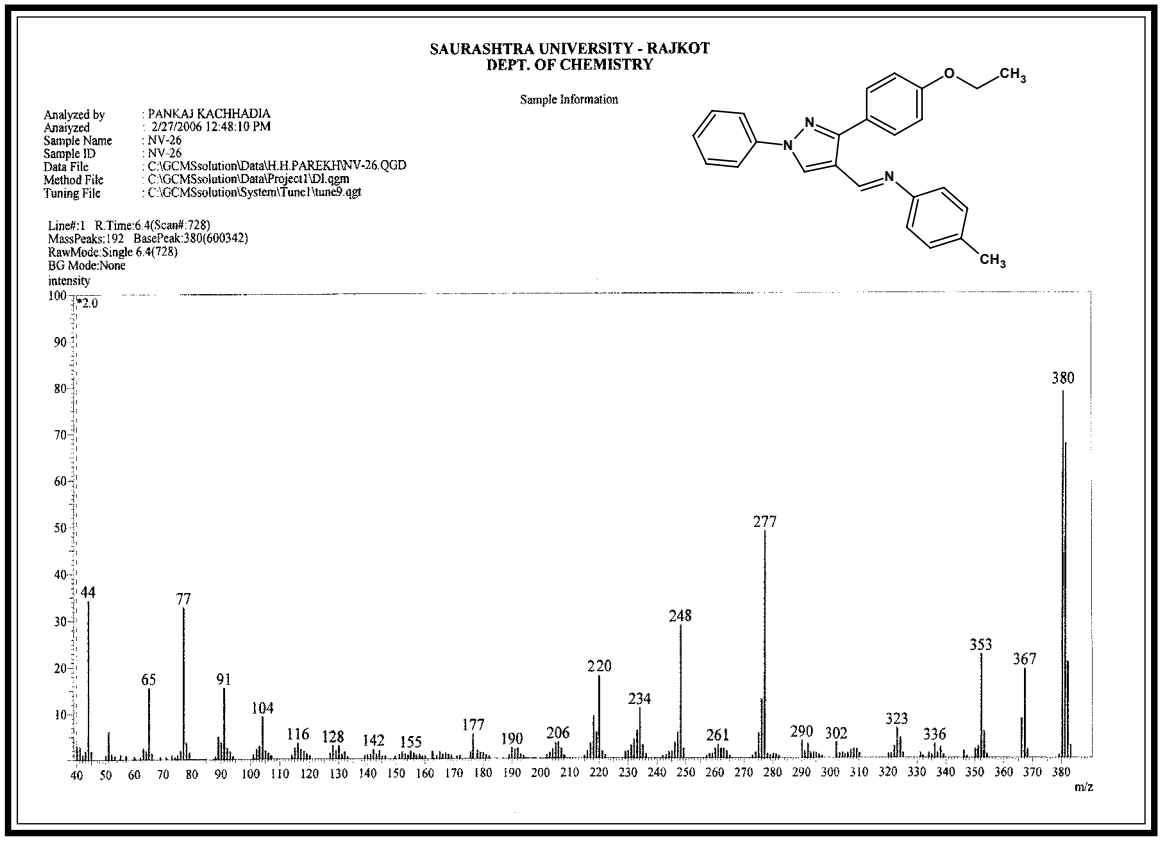


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.43-1.63	3H	triplet	$-OCH_2\underline{CH_3}$	J_{CH_3}=6.3
2.	4.06-4.11	2H	quartret	$-O\underline{CH_2}CH_3$	J_{CH_2}=7.0
3.	6.82-6.84	2H	doublet	Ar-$H_{gg'}$	J_{gf}=7.6
4.	6.99-7.01	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.7
5.	7.34-7.36	2H	triplet	Ar-H_{bd}	-
6.	7.47-7.51	3H	triplet	Ar-$H_{a,c,e}$	-
7.	7.60-7.62	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.7
8.	7.73	1H	singlet	CH_y	-
9.	7.76-7.78	2H	doublet	Ar-$H_{ff'}$	J_{fg}=7.6
10.	8.27	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





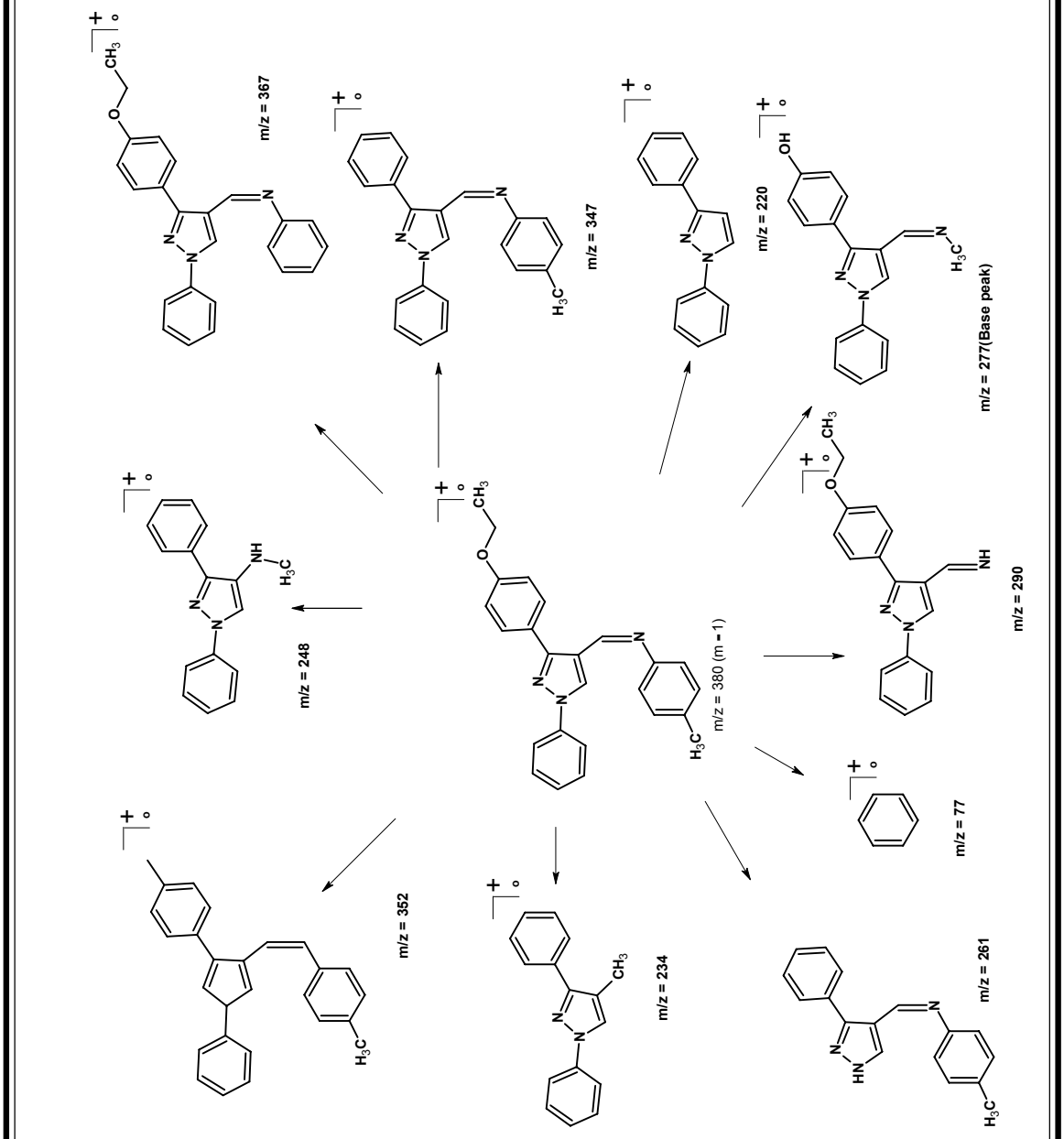
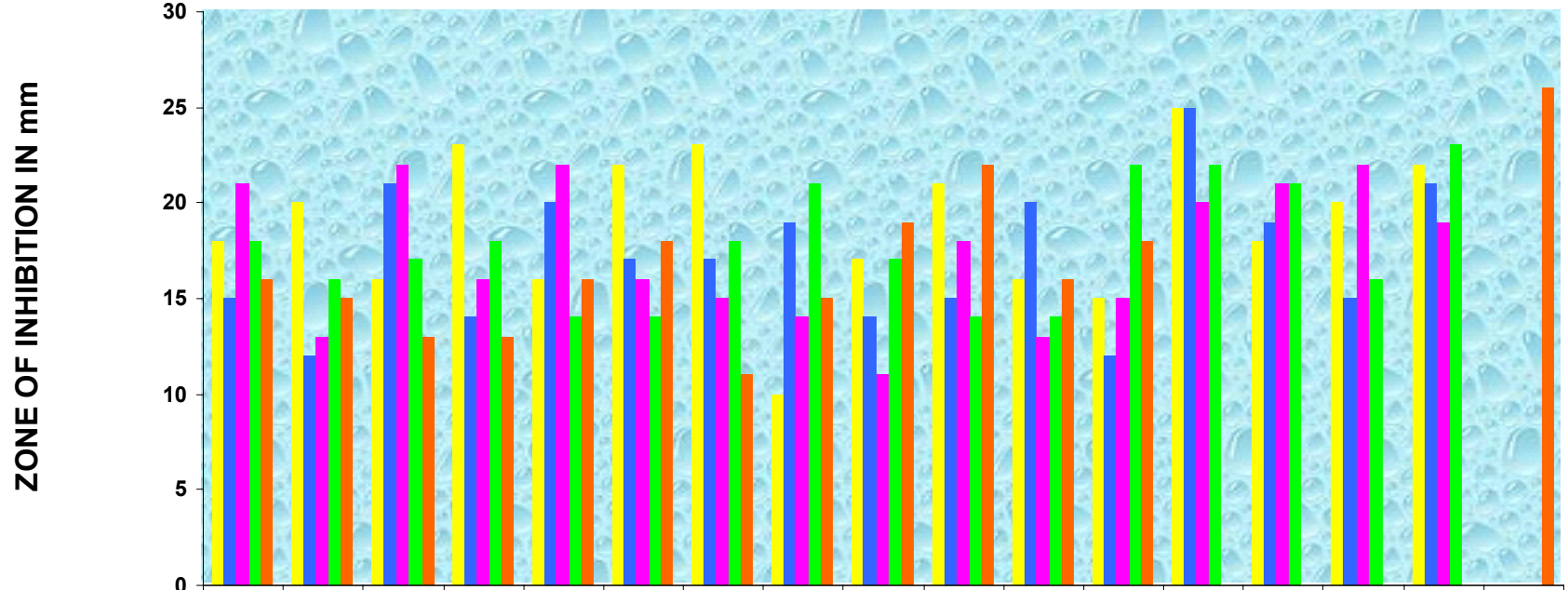

m/z = 380 (m - 1)
m/z = 367
m/z = 347
m/z = 220
m/z = 277(Base peak)
m/z = 290
m/z = 248
m/z = 352
m/z = 234
m/z = 77
m/z = 261

TABLE-7 : PHYSICAL CONSTANTS OF N-ARYL1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOL-4-YL-AZOMETHINES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
7a	C_6H_5-	$C_{24}H_{21}N_3O$	367	20	0.47	71	10.46	10.41
7b	4-OCH_3-C_6H_4-	$C_{25}H_{23}N_3O_2$	397	168	0.45	68	10.57	10.52
7c	4-CH_3-C_6H_4-	$C_{25}H_{23}N_3O$	381	159	0.52	60	11.02	10.96
7d	4-F-C_6H_4-	$C_{24}H_{20}FN_3O$	385	158	0.55	70	10.90	10.85
7e	4-Cl-C_6H_4-	$C_{24}H_{20}ClN_3O$	401	160	0.59	78	10.46	10.40
7f	4-Br-C_6H_4-	$C_{24}H_{20}BrN_3O$	446	154	0.53	73	9.41	9.35
7g	2-NO_2-C_6H_4-	$C_{24}H_{20}N_4O_3$	412	190	0.61	75	10.96	10.90
7h	3-NO_2-C_6H_4-	$C_{24}H_{20}N_4O_3$	412	205	0.50	58	10.26	10.21
7i	2-CH_3-C_6H_4-	$C_{25}H_{23}N_3O$	381	184	0.60	68	11.02	10.97
7j	2,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{19}Cl_2N_3O$	436	215	0.68	78	9.63	9.58
7k	3,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{19}Cl_2N_3O$	436	228	0.54	62	9.63	9.59
7l	2-OCH_3-C_6H_4-	$C_{25}H_{23}N_3O_2$	397	189	0.57	81	10.57	10.52

*TLC Solvent System :Ethylacetate : Hexane (2.7 :7.3)

GRAPHICAL CHART NO. 7 : ANTIMICROBIAL ACTIVITY OF N-ARYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL) PYRAZOL-4-YL- AZOMETHINES



	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Greseofulvin
B. coccus	18	20	16	23	16	22	23	10	17	21	16	15	25	18	20	22	0
S. aureus	15	12	21	14	20	17	17	19	14	15	20	12	25	19	15	21	0
E. aerogenes	21	13	22	16	22	16	15	14	11	18	13	15	20	21	22	19	0
P. aeruginosa	18	16	17	18	14	14	18	21	17	14	14	22	22	21	16	23	0
A. niger	16	15	13	13	16	18	11	15	19	22	16	18	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been concluded from the experimental data that the compounds bearing R=4-bromophenyl,2-nitrophenyl,2,4-dichlorophenyl and 4-fluorophenyl have displayed good activity against ***B.coccus***. The compounds bearing R=4-tolyl have shown considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains all the compounds were inactive against ***E. aerogenes*** except the compound bearing R=phenyl,4-tolyl and 4-chlorophenyl. While the compounds bearing R= 3-nitrophenyl and 2-anisyl showed significant activity against ***P. aeruginosa***.

ANTIFUNGAL ACTIVITY

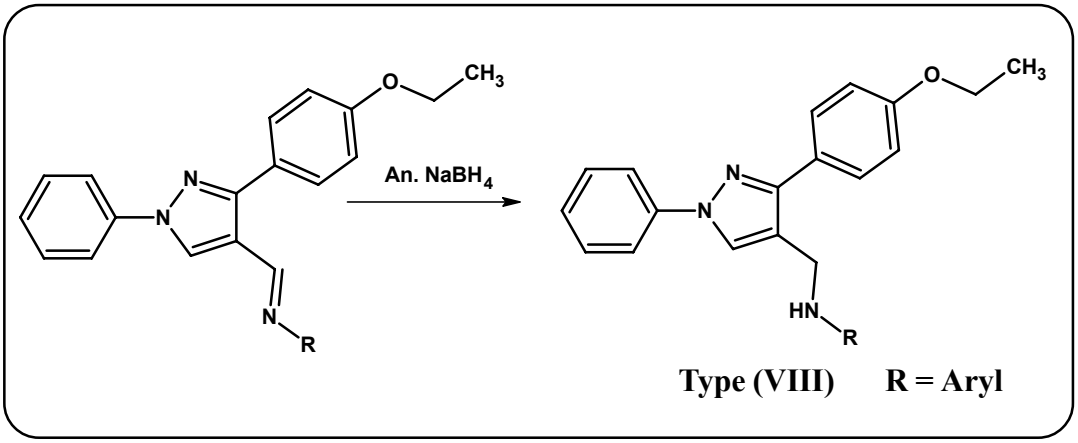
All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=2,4-dichlorophenyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drugs viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and greseofulvin.

SECTION - II

SYNTHESIS AND THERAPEUTIC EVALUATION OF 4-ARYLAMINOMETHYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOLES

The efficiency of arylaminomethyl derivatives as chemotherapeutic agents is well established. To further assess the pharmacological profile of such a class of compounds, we have synthesised arylaminomethyl derivatives of type (VIII) by selective reduction of (Imine group) shiff's base of (VII) with sodiumborohydride in controlled experimental condition as shown in the reaction scheme.

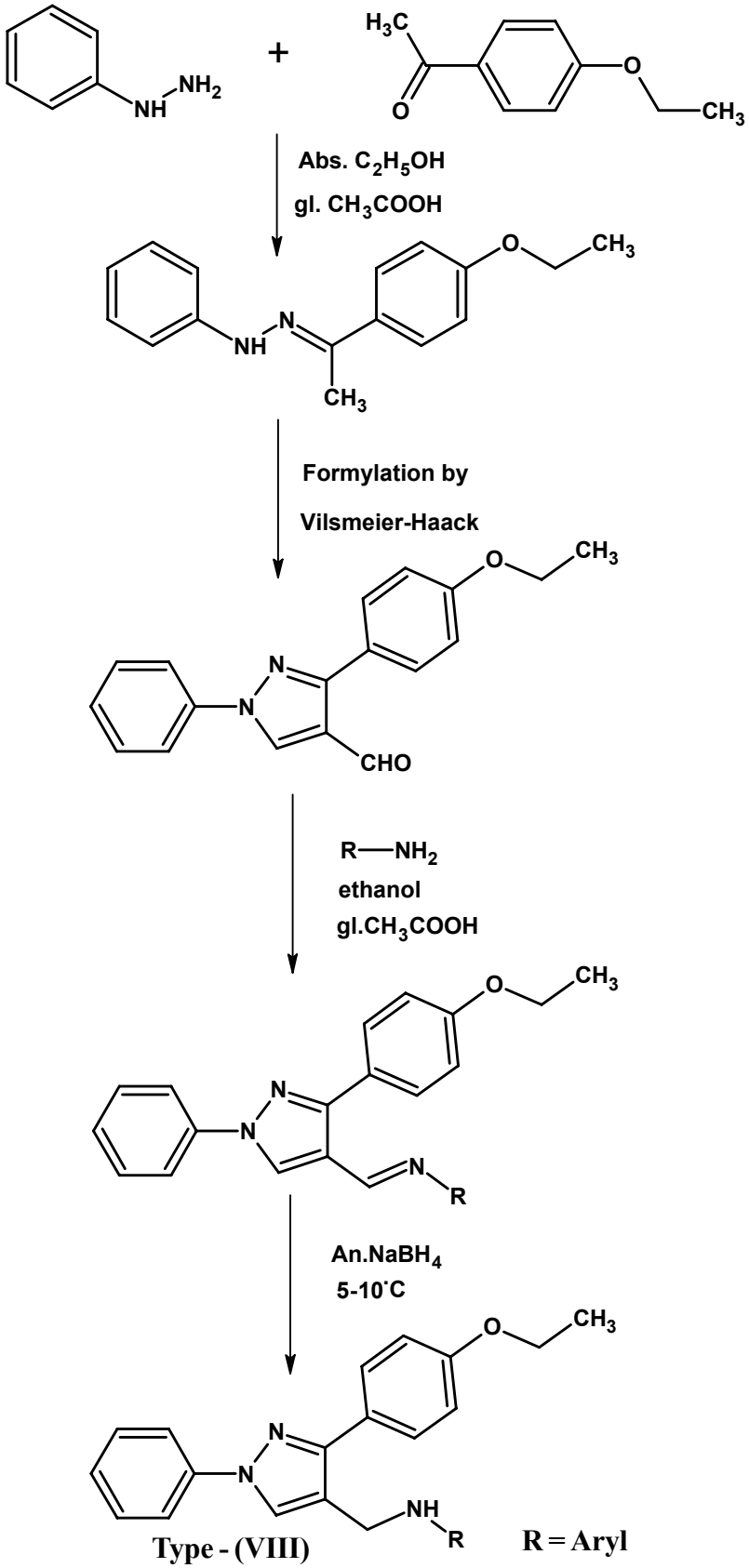


Type (VIII) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (VIII) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 4-ARYLAMINOMETHYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOLES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-(*p*-ethoxyphenyl)-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of N-Aryl-1,N-phenyl-3-(*p*-ethoxyphenyl)-pyrazol-4-yl-azomethines

See Part-VII, Section-I (C).

(D) Preparation of 4-(*p*-Fluorophenyl)aminomethyl-1,N-phenyl-3-(*p*-ethoxyphenyl)pyrazole

Sodium borohydride (0.15M, 0.57g) was added to a methanolic solution of N-(*p*-Flurophenyl)-1,N-phenyl-3-(*p*-ethoxyphenyl)-pyrazol-4-yl-azomethine (0.01M, 3.85gm) over a period of 30 minutes at temperature of 5-10^{o}C. The reaction mixture then kept over night at room tempeture. The excess of borohydride was neutralized by adding water and the product was extracted with ether.The ether extract was washed with water untill extract is neutralised, then dried over anhydrous Na_2SO_4 and finally the ether was evaporated to give aminomethyl derivative. Yield, 53%, m.p. 124^{o}C.($C_{24}H_{22}FN_3O$; Found : C, 74.11; H, 5.72; N, 13.85 %; Required : C, 74.07%; H, 5.67%; N, 13.80%).

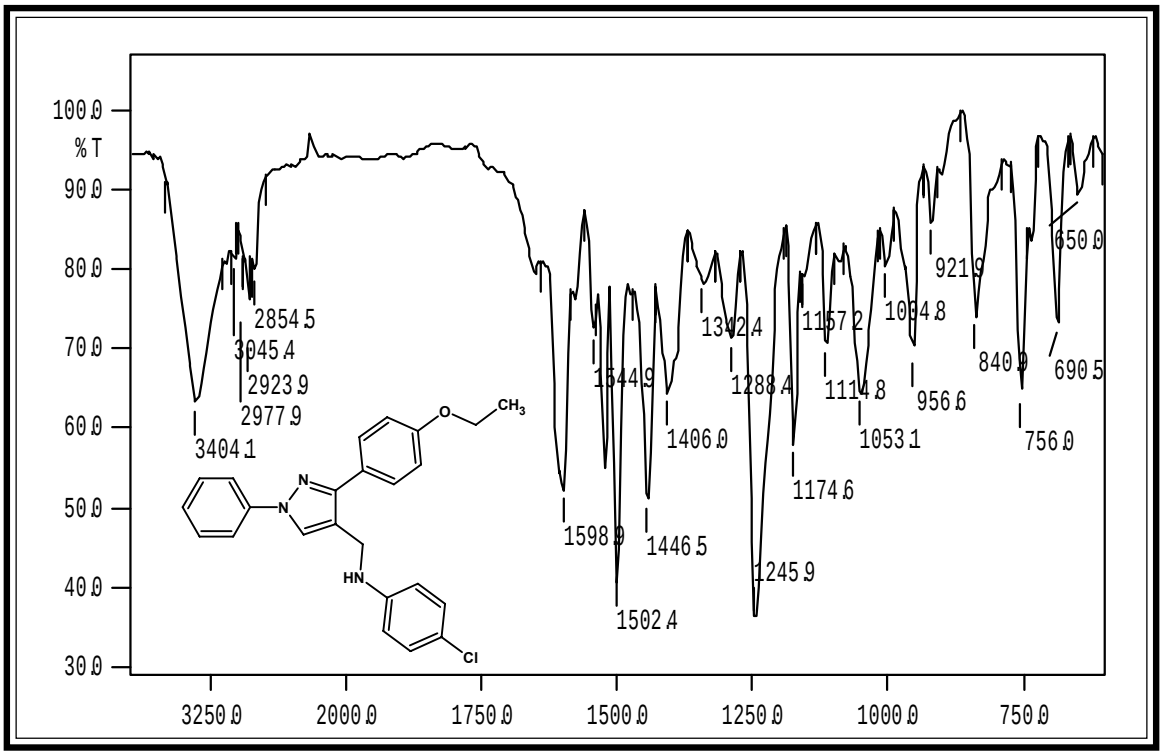
TLC solvent system : Ethylacetate:Hexane (1.5 : 8.5).

Similarly other substituted arylaminomethy pyrazoles have been prepared. The physical data are recorded in Table No.8.

(E) Antimicrobial activity of 4-Arylaminomethyl-1,N-phenyl-3-(*p*-ethoxyphenyl)pyrazole

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 8.

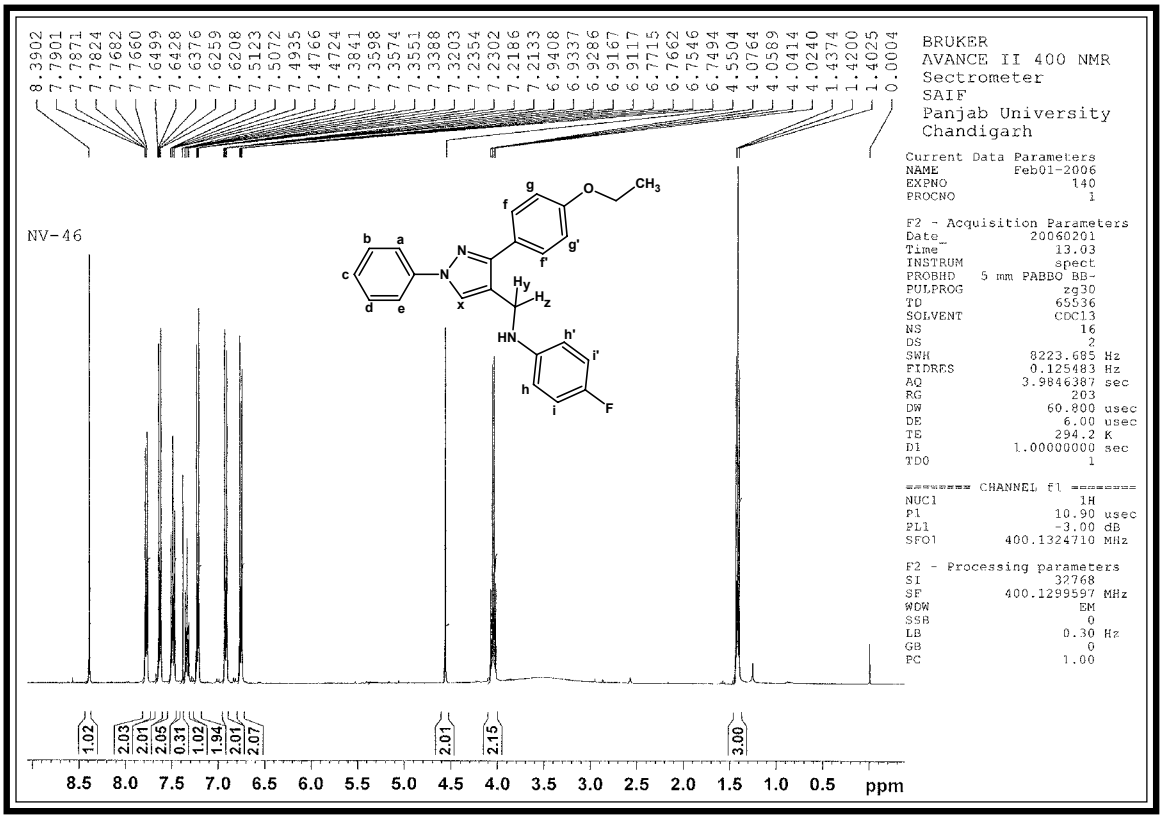
IR SPECTRAL STUDY OF 4-(*p*-CHLOROPHENYL)AMINOMETHYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOLE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	413
-CH_3	C-H str. (sym.)	2854	2880-2860	
	C-H i.p.def. (asym.)	1446	1470-1400	
	C-H o.o.p. def. (sym.)	1342	1390-1370	
Aromatic	C-H str.	3045	3080-3030	414
	C=C str.	1544	1585-1480	
	C-H i.p. def.	1114	1125-1090	
	C-H o.o.p. def	840	835-810	
Pyrazole	C=N str.	1598	1630-1590	415
moiety	C-N str.	1053	1230-1020	
	C-Cl str.	756	830-560	
Ether	C-O-C str. (asym.)	1245	1275-1200	413
	C-O-C str. (sym.)	1053 (overlapped)	1075-1020	
	C-N str.	1288		

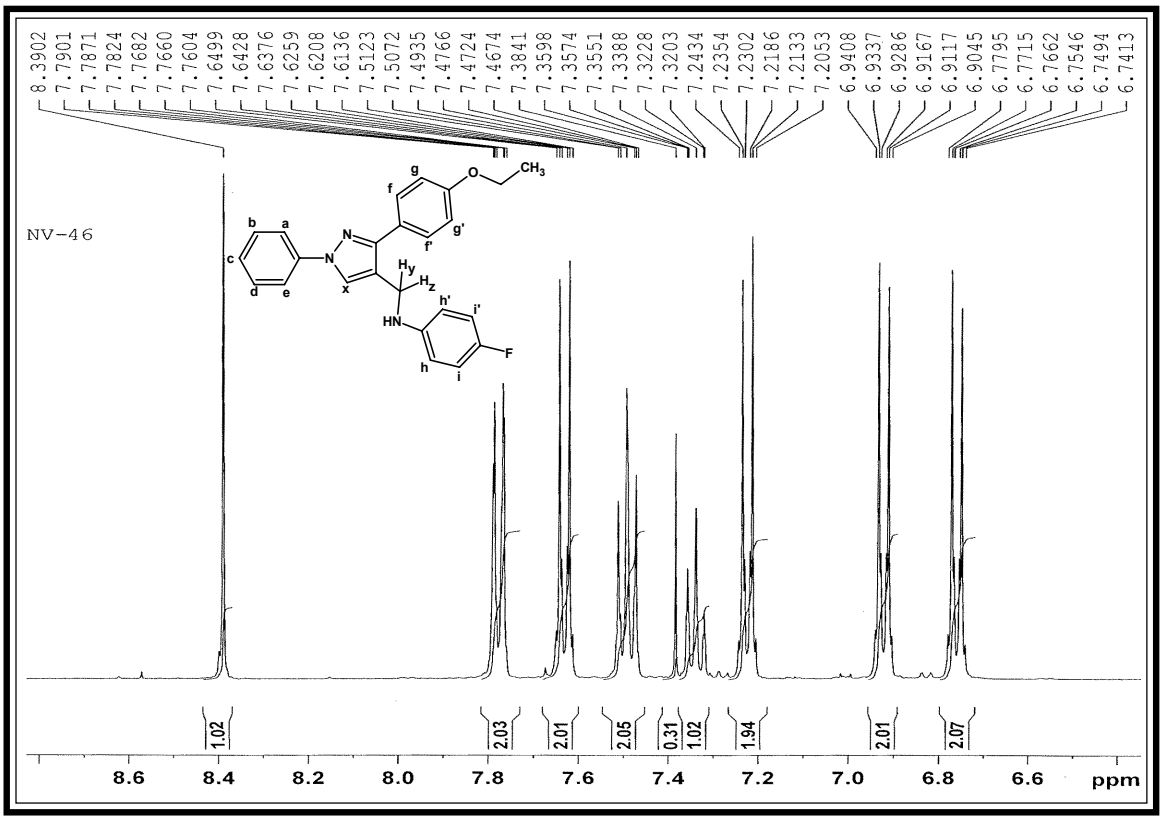
PMR SPECTRAL STUDY OF 4-(*p*-FLUOROPHENYL)AMINOMETHYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOLE

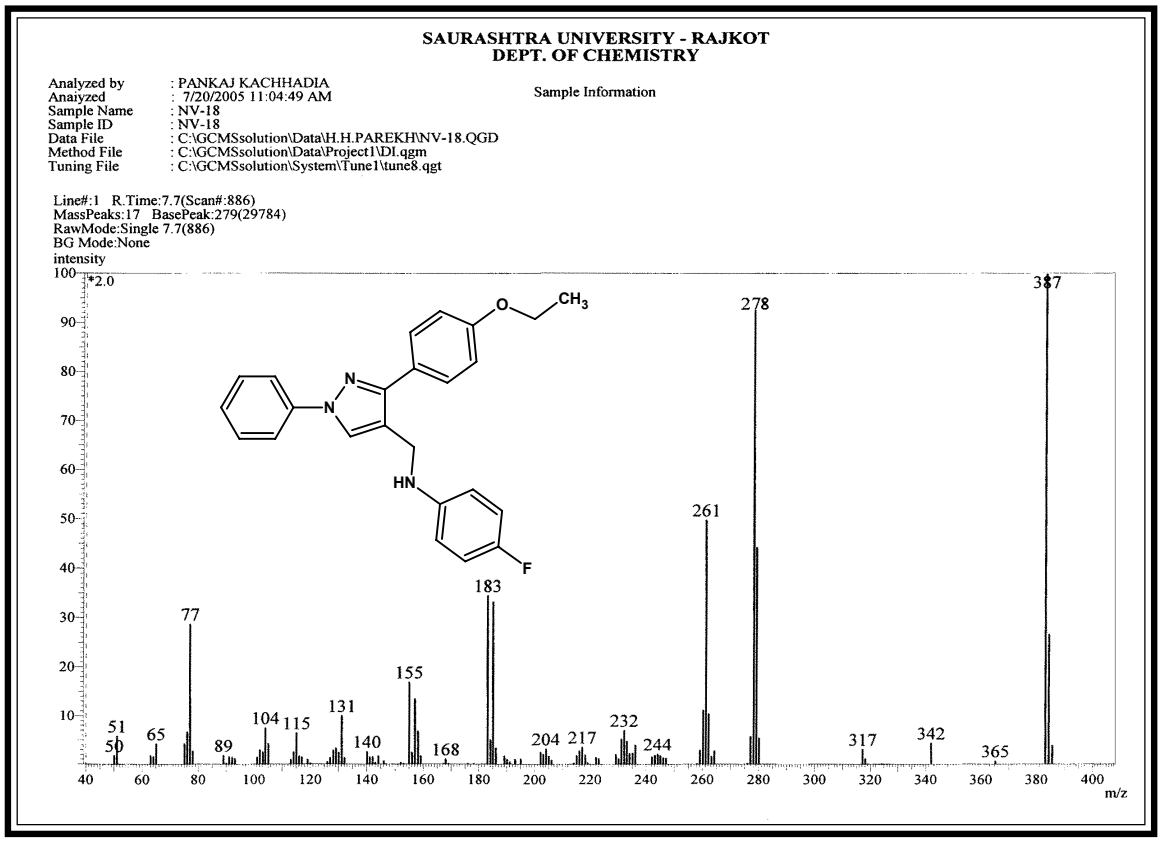


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.40-1.43	3H	triplet	$-OCH_2\underline{CH_3}$	J_{CH_3}=6.9
2.	4.02-4.07	2H	quartret	$-O\underline{CH_2}CH_3$	J_{CH_2}=7.0
3.	4.55	2H	singlet	$CH_{Y,Z}$	-
4.	6.74-6.76	2H	doublet	Ar-$H_{gg'}$	J_{gh}=8.2
5.	6.91-6.93	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.4
6.	7.21-7.23	2H	doublet	Ar-H_{ae}	J_{ab}=8.5
7.	7.32-7.35	1H	triplet	Ar-H_c	-
8.	7.46	1H	singlet	NH	-
9.	7.47-7.51	2H	triplet	Ar-H_{bd}	-
10.	7.62-7.64	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.2
11.	7.76-7.78	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.4
12.	8.39	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION





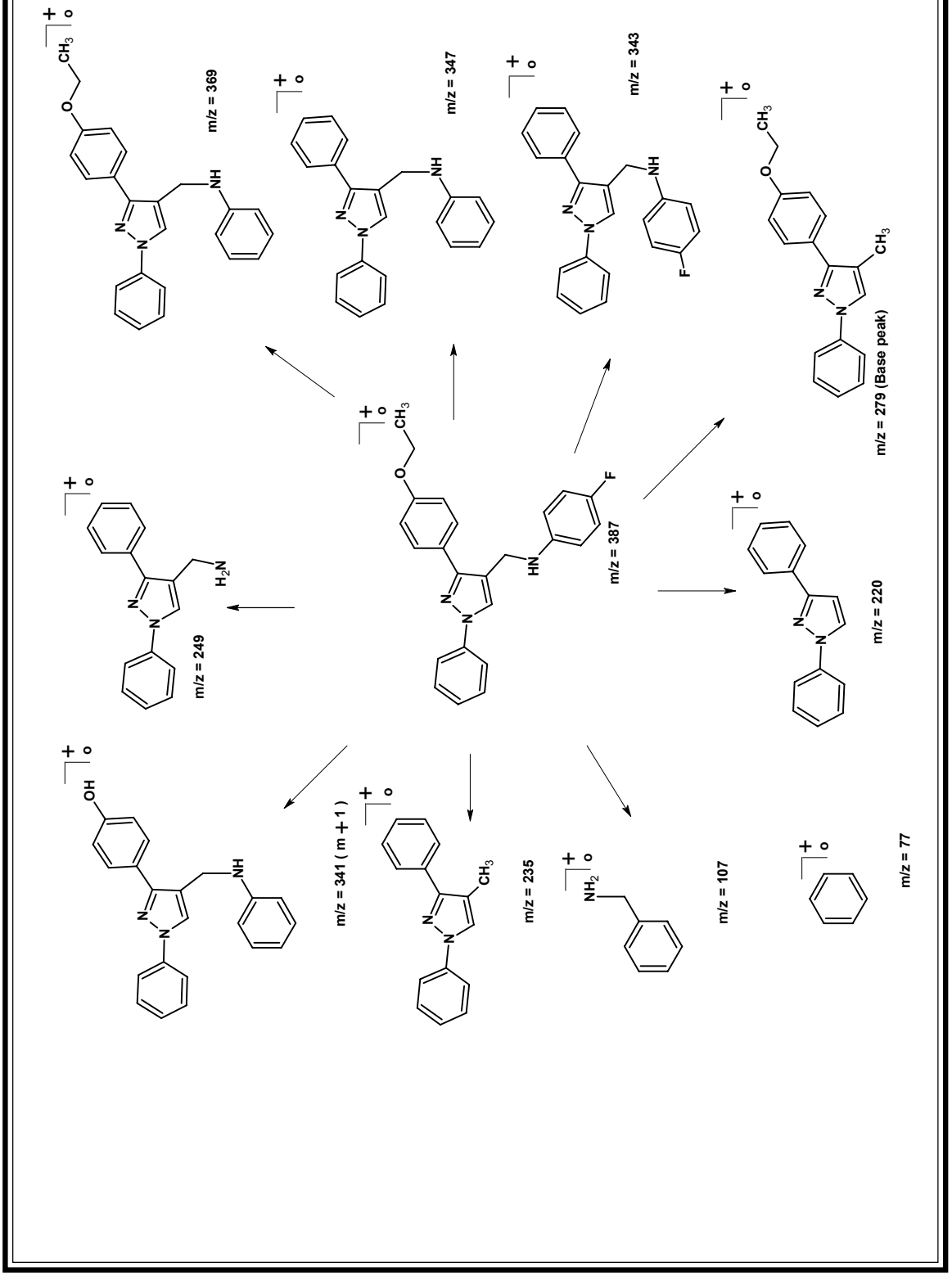
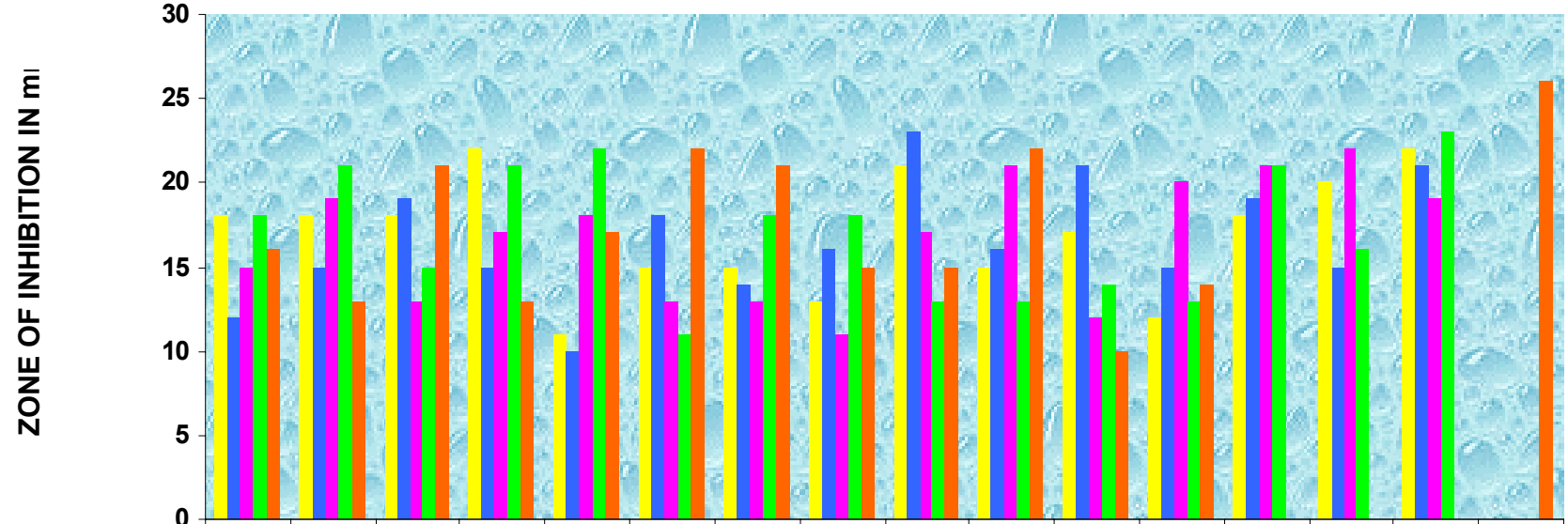

m/z = 369
m/z = 347
m/z = 343
m/z = 279 (Base peak)
m/z = 249
m/z = 387
m/z = 220
m/z = 341 (m + 1)
m/z = 235
m/z = 107
m/z = 77

TABLE-8 : PHYSICAL CONSTANTS OF 4-ARYLAMINOMETHYL-1,N-PHENYL-3-(*p*-ETHOXYPHENYL)-PYRAZOLES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
8a	C_6H_5-	$C_{24}H_{23}N_3O$	369	110	0.52	56	11.37	11.32
8b	4-OCH_3-C_6H_4-	$C_{25}H_{25}N_3O_2$	399	145	0.63	57	10.52	10.47
8c	4-CH_3-C_6H_4-	$C_{25}H_{25}N_3O$	383	120	0.58	61	10.96	10.93
8d	4-F-C_6H_4-	$C_{24}H_{22}FN_3O$	387	124	0.51	53	13.85	13.80
8e	4-Cl-C_6H_4-	$C_{24}H_{22}ClN_3O$	403	135	0.49	63	10.40	10.35
8f	4-Br-C_6H_4-	$C_{24}H_{22}BrN_3O$	448	140	0.56	55	9.37	9.33
8g	2-NO_2-C_6H_4-	$C_{24}H_{22}N_4O_3$	414	115	0.70	59	13.52	13.47
8h	3-NO_2-C_6H_4-	$C_{24}H_{22}N_4O_3$	414	132	0.69	62	13.52	13.47
8i	2-CH_3-C_6H_4-	$C_{25}H_{25}N_3O$	383	146	0.52	53	10.96	10.91
8j	2,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{21}Cl_2N_3O$	438	140	0.64	49	9.59	9.53
8k	3,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{21}Cl_2N_3O$	438	158	0.68	55	9.59	9.55
8l	2-OCH_3-C_6H_4-	$C_{25}H_{25}N_3O_2$	399	126	0.64	58	10.52	10.47

*TLC Solvent System :Ethylacetate : Hexane (1.5 : 8.5)

GRAPHICAL CHART NO. 8 : ANTIMICROBIAL ACTIVITY OF 4-ARYLAMINOMETHYL-1,N-PHENYL - 3 - (*P* - ETHOXYPHENYL)-PYRAZOLES



	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8k	Benzoylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	18	18	18	22	11	15	15	13	21	15	17	12	18	20	22	0
S. aureus	12	15	19	15	10	18	14	16	23	16	21	15	19	15	21	0
E. aerogenes	15	19	13	17	18	13	13	11	17	21	12	20	21	22	19	0
P. aeruginosa	18	21	15	21	22	11	18	18	13	13	14	13	21	16	23	0
A. niger	16	13	21	13	17	22	21	15	15	22	10	14	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

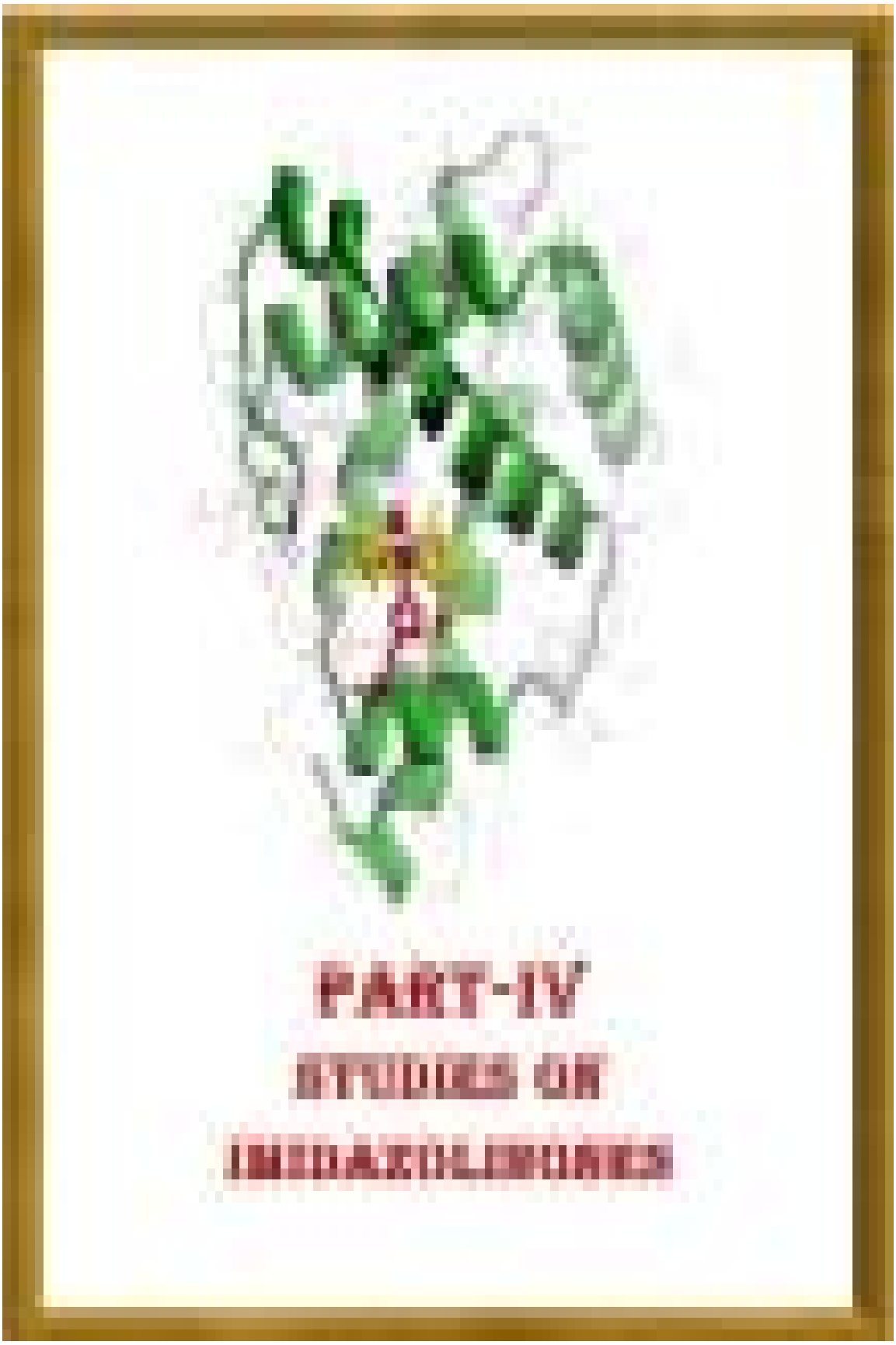
It has been concluded from the experimental data that the compounds bearing R=4-fluorophenyl and 2-tolyl have displayed good activity against ***B.coccus***. The compounds bearing R= 2-tolyl,3,4-dichlorophenyl have shown considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains all the compounds were inactive against ***E. aerogenes*** except the compound bearing R=2,4-dichlorophenyl.While the compounds bearing R=4-chlorophenyl,4-fluorophenyl and 4-anisyl showed significant activity against ***P. aeruginosa***.

ANTIFUNGAL ACTIVITY

All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=4-bromophenyl,4-tolyl,2,4-dichlorophenyl and 2-nitrophenyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drugs viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.



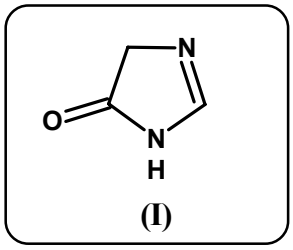
PART-IV

STUDIES ON

IMIDAZOLIDINES

INTRODUCTION

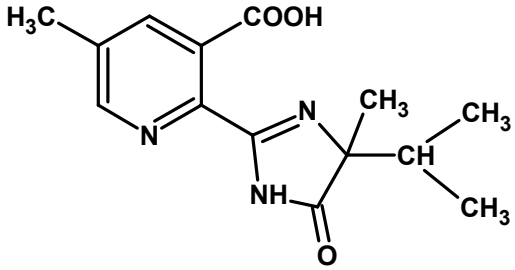
*T*he five membered heterocyclic ring system 5-oxo-imidazolines have two nitrogen atom at 1- and 3-positions and a carbonyl group at 5-position.



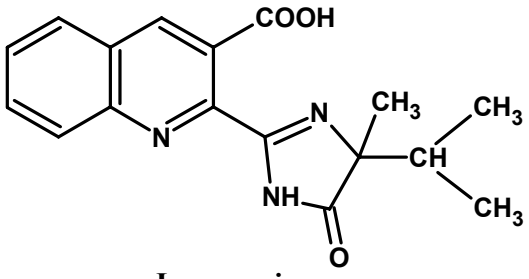
(I)

A. W. Hoffman[191] for the first time discovered 5-oxo-imidazoline by heating N'-diacetylethylene diamine in a steam of dry hydrogen chloride. A.Ladenburg[192] prepared the same compound by fusing two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride.

The drug molecules containing imidazolinone ring system are as under.



Imazapic



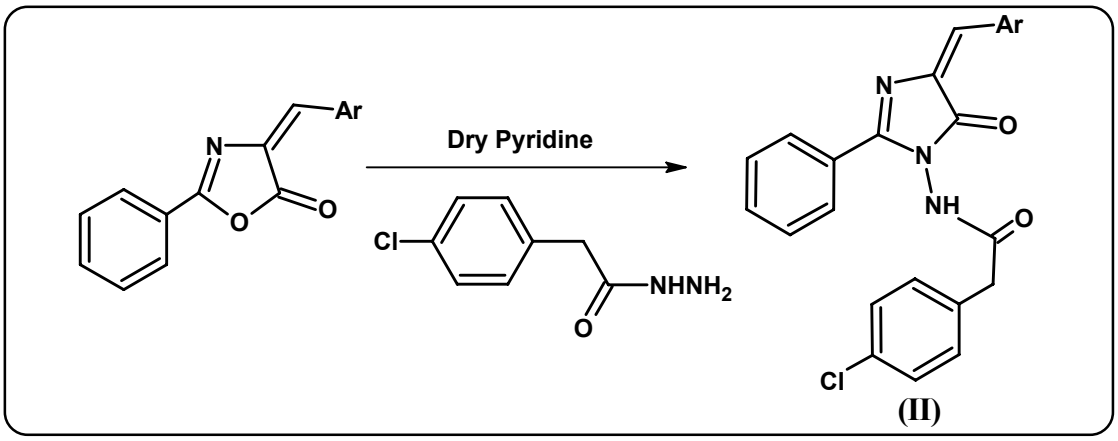
Imazaquin

SYNTHETIC ASPECTS

Various methods have been reported for the synthesis of imidazolinones in literature.[193] Aminolysis of oxazolone with amine leads to the formation of imidazolinones which has been reported in literature.[194]

1. Allimony et al.[195] have synthesized new imidazolinone derivatives by conventional method.

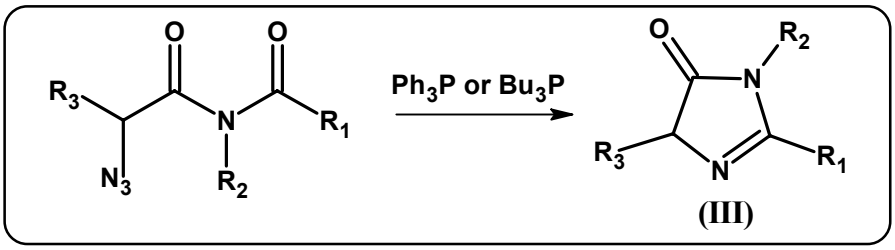
2. A. Saxena et al.[196] have synthesized new imidazolinones (II).



(II)

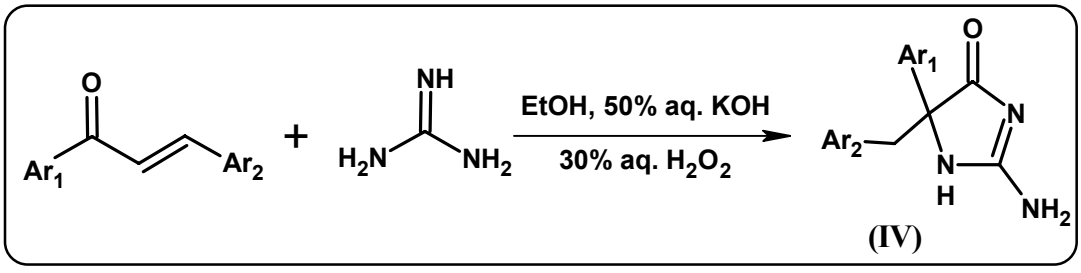
3. Feng-Jun-Cai et al.[197] have reported 5-imidazolinone derivatives by microwaves irradiation.

4. Hisato Takeuchi et al.[198] have synthesised imidazolinones by the reaction of azido substituted imides with triphenylphosphine or tributylphosphine.



(III)

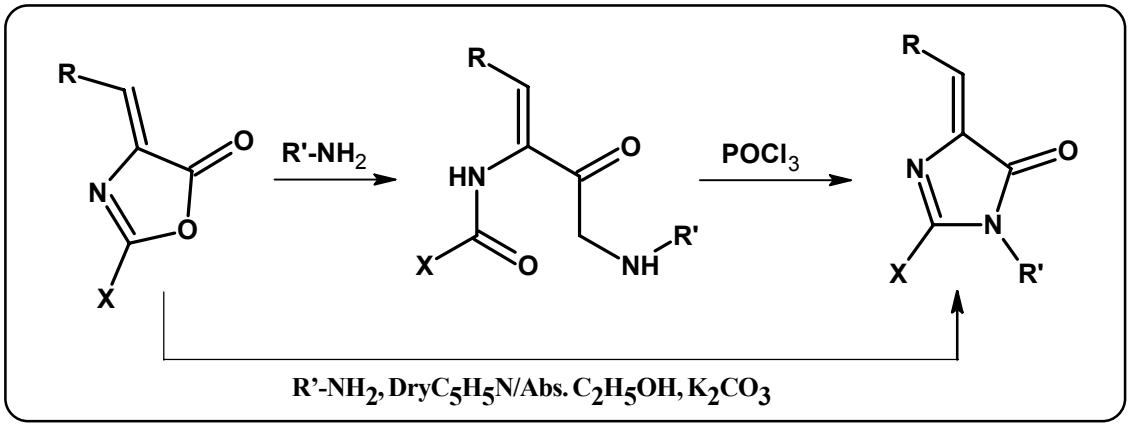
5. Laszlo Varga et al.[199] have synthesized imidazolinones (IV) by the reaction of chalcone and guanidine.



(IV)

MECHANISM

Azalactone reacts with variety of compounds such as water, alcohols, amines and hydrogen halides. Amides of a-acylamino acryclic acids obtained from the condensation of azalactone and primary amines can be converted into imidazolinones as shown in equation. The ring closure can be affected under a variety of conditions. Substituted anilides have been converted to imidazolinone derivatives by the action of $POCl_3$.



THERAPEUTIC IMPORTANCE

Naphazoline hydrochloride, xylometazoline hydrochloride etc. are various imidazolinone derivatives which have been used as adrenergic stimulants and tolazoline and phenotolamine as adrenergic blocking agents. Various imidazolinones are known to exhibit a broad spectrum of biological activities such as,

(a) Anticonvulsant[200],

(b) Antiinflammatory[201-203]

(c) Antimicrobial[204]

(d) Antiviral[205]

(e) Antiparkinsonian[206,207]

(f) Anthelmintic[208]

(g) Antihistaminic[209]

(h) Anticancer[210,211]

(i) Antidiabatic[212]

(j) Bactericidal[213]

(k) Glucagon antagonists[214]

(l) Hypertensive[215]

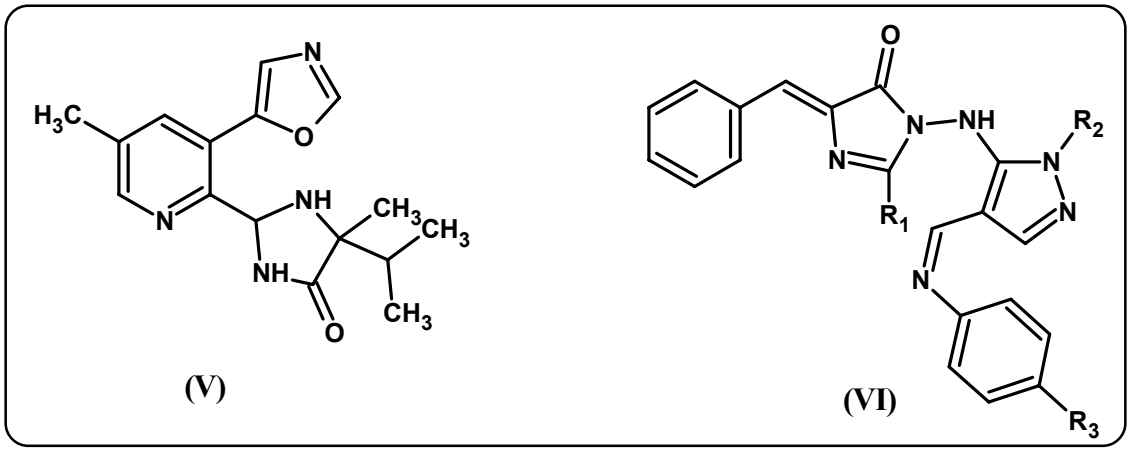
(m) Fungicidal[216,217]

(n) Insecticidal[218]

(o) Potent CNS depressant[219,220]

(p) Thrombin inhibitor[221]

V. Akyoshi et. al.[222] have prepared some new imidazolinone derivatives (V) and reported their herbicidal activity. Agrochemical activity of imidazolinones have been reported by Kolhe and co-workers[223].

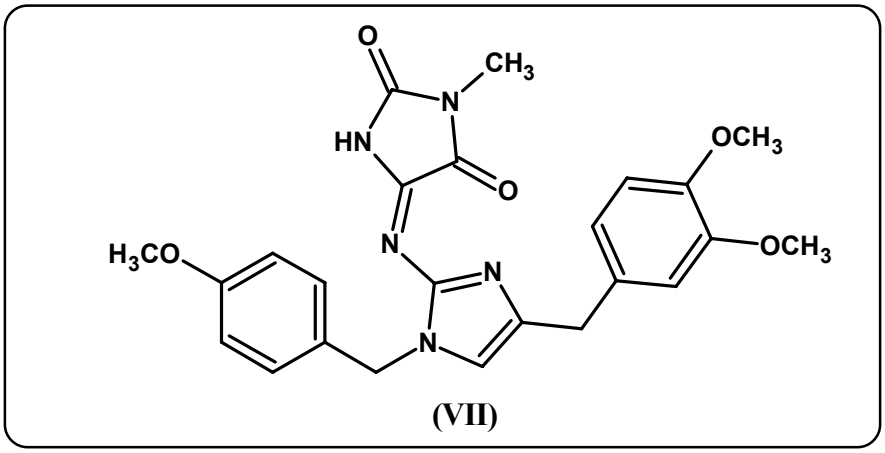


Antifungal activity of imidazolinones towards *Aspergillus fumigutus* is investigated by T. Kitazaki et . al[224]. Ozaki Satoshi et. al.[225] have reported imidazolinones useful as analgesic, antagonists against tolerance to narcotic analgesics typified by morphine, agents for the treatment of obesity and drugs for ameliorating brain function. Lacroix Guy et. al.[226] have synthesised 5-imidazolinones as possible agrochemical fungicide. Rama Sharma and co-workers[227] have formulated 5-oxo-imidazolines possessing potential antimicrobial activity.

K. K. Awasthi et. al.[228] (VI) have synthesised some new imidazolinone derivatives and reported their antimicrobial activity.

Imam Hidayat et. al.[229] have reported ALS-inhibitory activity of imidazolinones. Keun-Jin Oh et. al.[230] have investigated some imidazolinone derivatives which possess the enzymatic activity as well as the binding affinity for the cofactor FAD (Flavin adenine dinucleotide). Stefama Lauter and Co-worker[231] have isolated imidazoline by using different methods and tested for the treatment of cytokine release. Imidazoline derivatives have been prepared by Declera and co-worker[232] showing anti-HIV activity.

Ding, Ming-Wu et. al.[233] have prepared novel imidazolines and reported their antifungal activity. Irene M. L. et. al.[234] have investigated some imidazolinone derivatives possessing antireteroviral activity. Zhong Jin[235] has found imidazoline derivatives (VII) as cytotoxic towards several tumor cell lines.



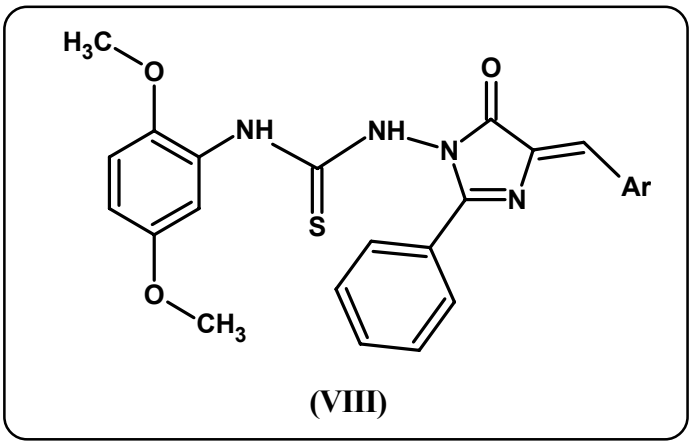
(VII)

Jean M. R. et. al.[236] have discovered imidazolinones and tested as antileishmanial agents.

CONTRIBUTION FROM OUR LABORATORY

Dr. H. H. Parekh and co-workers[237] have synthesised 5-oxo-imidazolines as novel bioactive compounds derived from benzimidazole. Parikh et. al.[238] have reported 4-(4'-arylidene-2'-phenyl-5'-oxo-imidazolin-1'-yl)-benzophenone and screened for their antimicrobial activity. A. R. Parikh et.al.[239] have reported 5-oxo-imidazolines as biologically active agents. Hasmukh Kanjaria and co-workers[240] have described imidazolinones as potential antimicrobial agents.

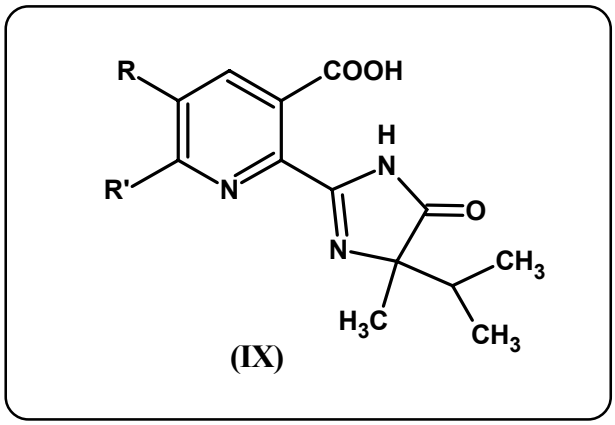
Dr. H. H. Parekh et. al.[241] suggested imidazolinones as a antitubercular and anticancer (VIII) agents.



(VIII)

Satyen P. Patel and co-workers[242] have synthesised imidazolines as biologically active agents. Joshi H. et. al.[243] have synthesised imidazolinones as potent anticonvulsant agents.

Recently, Aleksey N. Vasiliev et. al.[244] have synthesised imidazolinone derivatives (IX) and reported their herbicidal activity.



(IX)

C. Alister and co-workers[245] have documented herbicidal activity of imidazolinone derivatives. E. Jayachandran et. al.[246] have reported imidazolinones as antimicrobial agents. Imidazolinone derivatives as acetohydroxyacid synthase (AHAS) inhibitors have been suggested by Tan S. and co-workers[247].

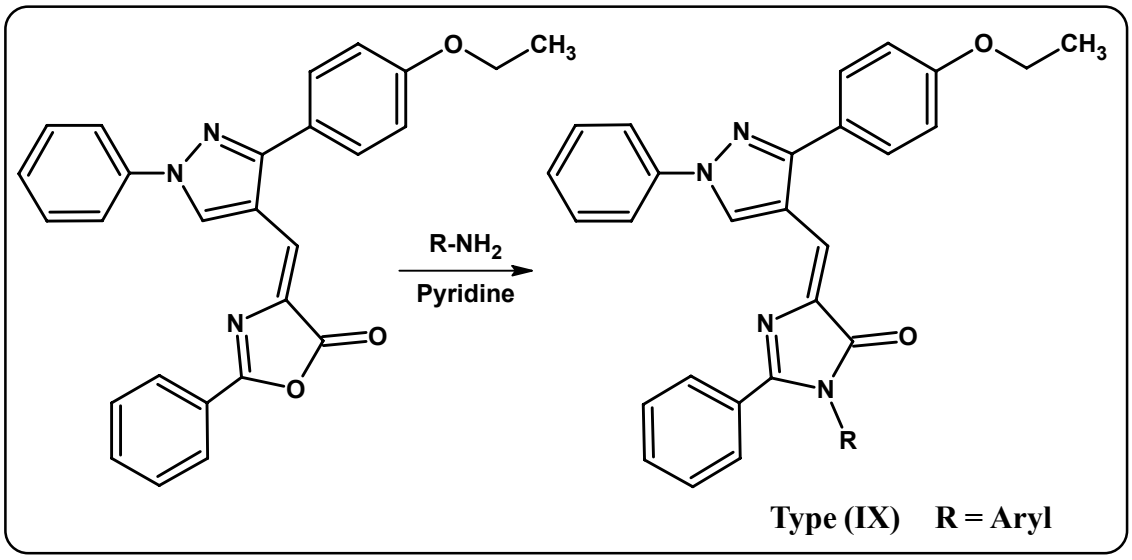
The development of efficient and selective synthesis of imidazolinones has attracted increasing attention because they often bring about unique pharmacodynamic activities. In search of biologically potent imidazolinone derivatives, it was considered worthwhile to synthesise imidazolinones which have been described as under.

SECTION I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXY-PHENYL-4'-PYRAZOLYLMETHINE)-IMIDAZOLIN-5-ONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-4'-PYRAZOLYLMETHINE)-IMIDAZOLIN-5-ONES

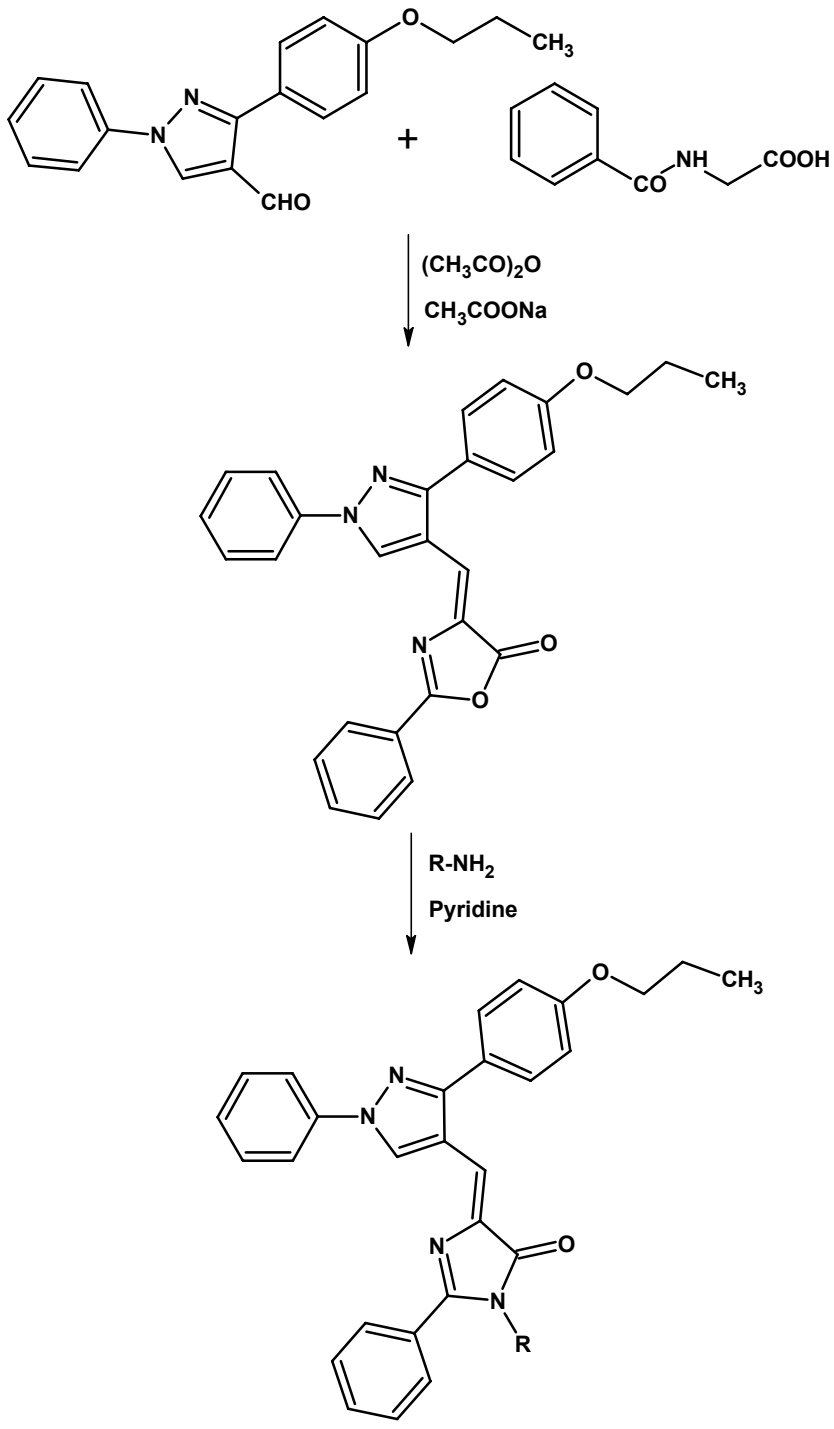
Imidazolinone derivatives possess varieties of biological and pharmacological properties. Here, we report the synthesis of some new 5-oxo-imidazolines of type (IX). The strategy employed for the synthesis of desired compounds involved the condensation of azlactones with different aromatic amines shown as under.



The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (IX)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-4'-PYRAZOLYLMETHINE)-IMIDAZOLIN-5-ONES

(A) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(B) Synthesis of 2-Phenyl-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-oxazolin-5-one

A mixture of 1,N-phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole (2.92 g, 0.01M), acetic anhydride (7.6ml, 0.075M), sodium acetate (2.0 g, 0.025M) and hippuric acid (4.4g, 0.025M) was heated on waterbath for 4 hrs. Resulting mass was poured onto crushed ice, filtered, washed with hot water and crystallised from ethanol. Yield 65%, m.p.143^{O}C, ($C_{27}H_{11}N_3O_3$: Required C : 74.47; H : 4.86; N: 9.65; Found C : 74.40; H : 4.80; N : 9.61%).

TLC solvent system : Ethyl acetate : Hexane (1.5 : 8.5)

(C) Synthesis of 1,N-*p*-Chlorophenyl-2-phenyl-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-imidazolin-5-one

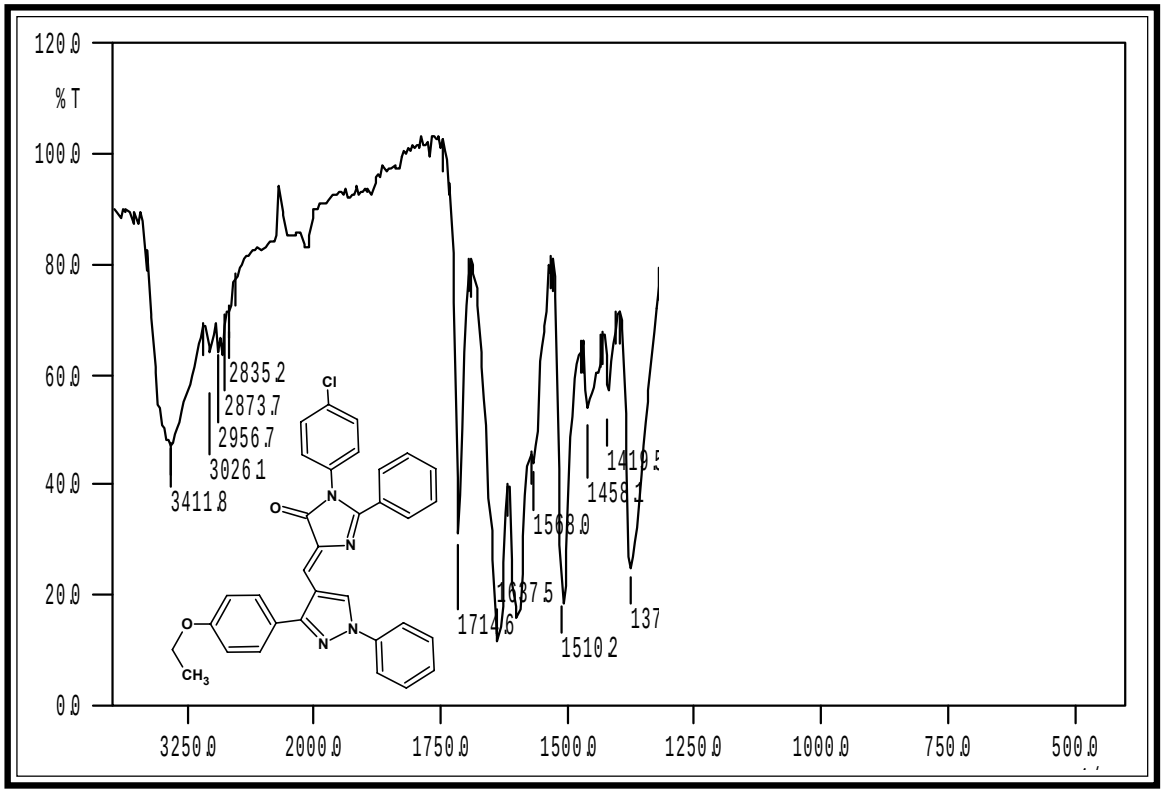
A mixture of 2-phenyl-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-4'-pyrazolylmethino)-oxazolin-5-one (4.35 g, 0.01M) and *p*-chloroaniline(1.06g, 0.01M) in dry pyridine (20 ml) was refluxed for 12 hrs. Resulting mass was poured on to crushed ice and neutralised with HCl, filtered and crystallised from DMF. Yield, 60%, m.p.170^{O}C ($C_{33}H_{25}ClN_4O_2$: Required C: 72.72; H: 4.62; N: 10.28; Found : C: 72.68; H: 4.57; N: 10.23%).TCL solvent system : Acetone : Benzene (1.5 :8.5).

Similarly other imidazolin-5-ones have been prepared. The physical data are recorded in Table No. 9.

(D) Antimicrobial activity of 1,N-Aryl-2-phenyl-4-(1',N-phenyl-3'-*p*-ethoxy phenyl-4'-pyrazolylmethine)- imidazolin-5-ones

Antimicrobial testing was carried out as described in [A] Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 9

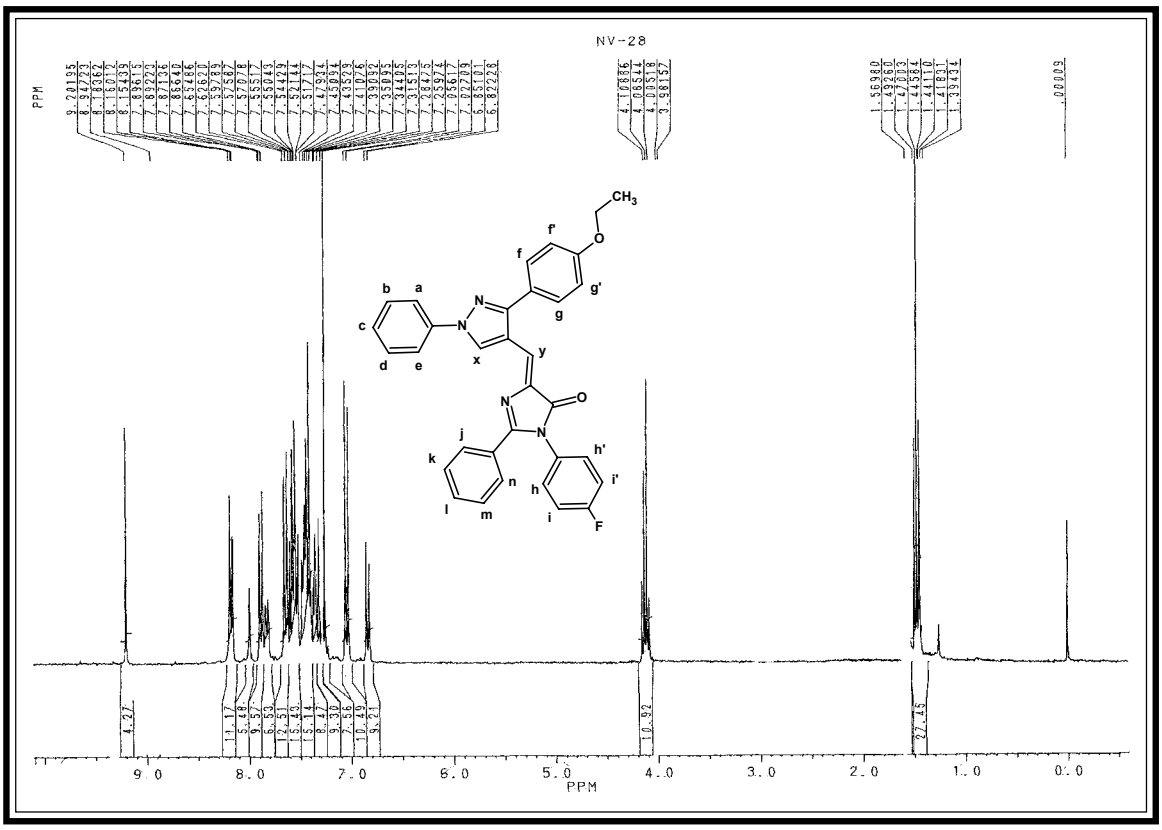
IR SPECTRAL STUDY OF 1,N-*p*-CHLOROPHENYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2956	2975-2950	413
-CH_3	C-H str. (sym.)	2873	2880-2860	
	C-H i.p.def. (asym.)	1458	1470-1435	
	C-H o.o.p. def. (sym.)	137	1390-1370	
Aromatic	C-H str.	3026	3080-3030	
	C=C str.	1510	1585-1480	414
	C-H i.p. def.	1105	1125-1090	
	C-H o.o.p. def	827	835-810	
Pyrazole	C=N str.	1568	1630-1560	415
moiety	C-N str.	1166	1230-1020	
Ether	C-O-C str. (asym.)	1257	1275-1200	413
	C-O-C str. (sym.)	1058	1075-1020	
Imidazolinone	C=O str.	1714	1770-1655	414
ring	C=N str.	1637	1650-1550	
	C-N str.	1257	1260-1220	
	C-Cl str.	779	800-750	

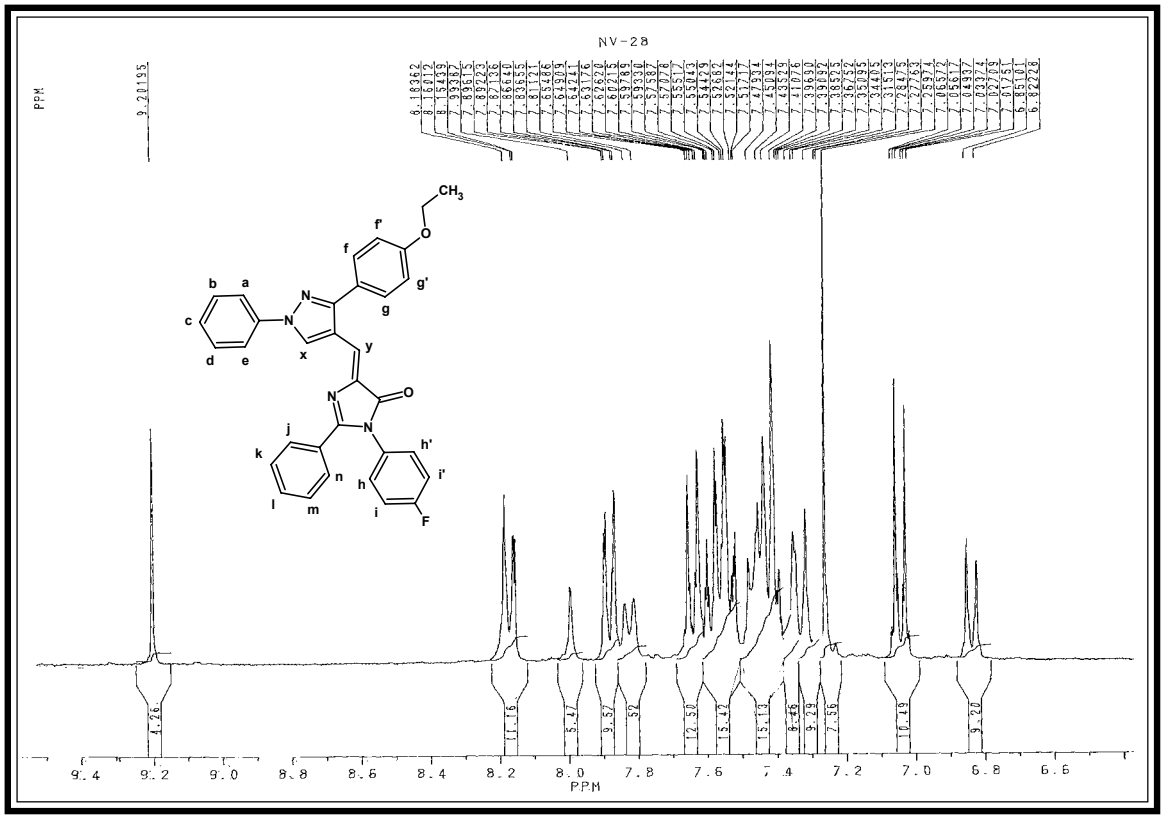
PMR SPECTRAL STUDY OF 1,N-*p*-FLUOROPHENYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.44-1.47	3H	triplet	$-OCH_2\underline{C}H_3$	J_{CH_3}=6.7
2.	3.98-4.10	3H	quartet	$-O\underline{C}H_2CH_3$	J_{CH_2}=7.0
3.	6.82-6.85	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.6
4.	7.04-7.06	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.8
5.	7.36-7.41	2H	doublet	Ar-H_{jn},	J_{jk}=8.7
6.	7.41-7.47	3H	multiplet	Ar-$H_{b,c,d}$	-
7.	7.55-7.62	3H	multiplet	Ar-$H_{k,l,m}$	-
8.	7.62-7.64	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.8
9.	7.87-7.89	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.6
10.	7.99-7.89	1H	singlet	CH_y	
11.	8.15-8.17	2H	doublet	Ar-H_{ae}	J_{ab}=8.7
12.	9.20	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION



IR SPECTRAL STUDY OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-(*p*-ETHOXYPHENY-4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONES

Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

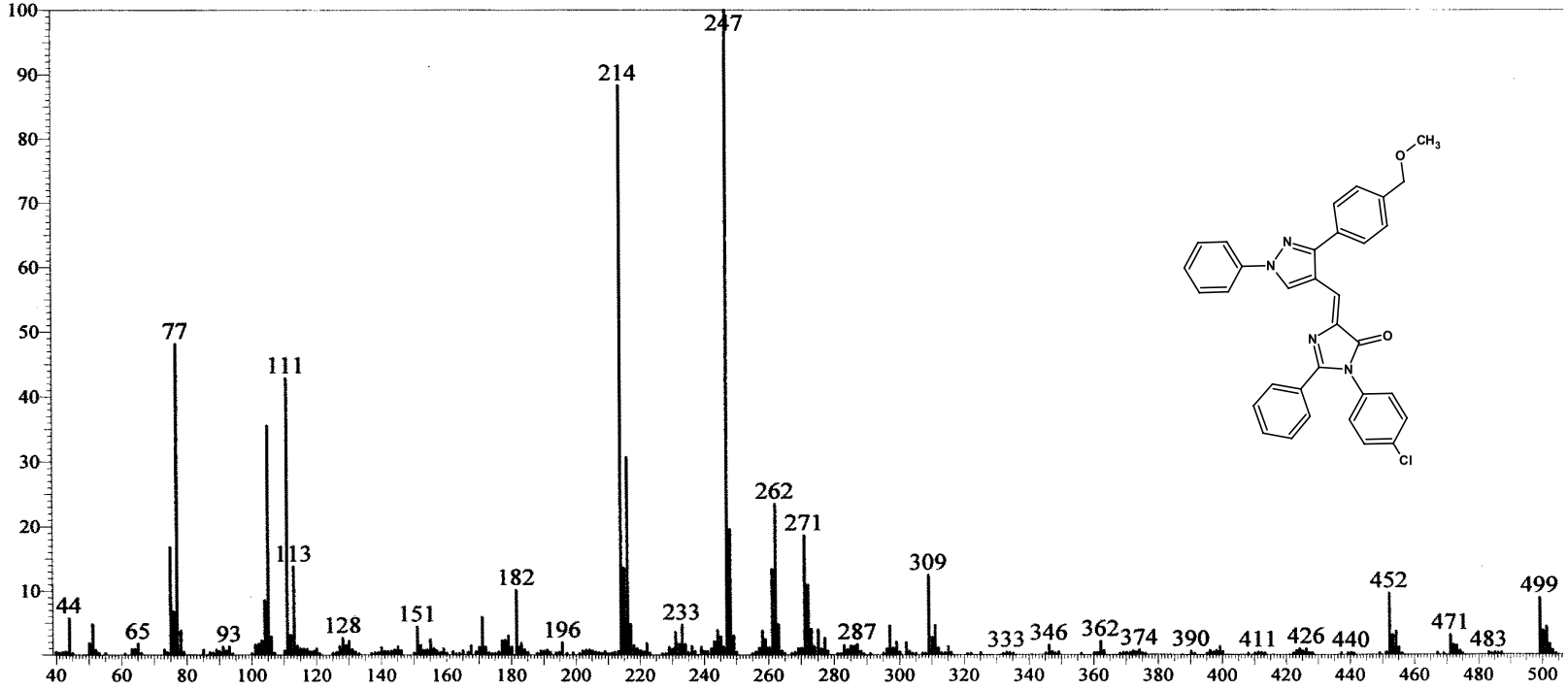
Sr. No.	R	C=O str.
11a	C_6H_5-	1718
11b	4-Cl-C_6H_4-	1714
11c	4-Br-C_6H_4-	1715
11d	4-F-C_6H_4-	1720
11e	4-NO_2-C_6H_4-	1716
11f	3-NO_2-C_6H_4-	1708
11g	3-Cl,4-F-C_6H_3	1714
11h	4-OCH_3-C_6H_4-	1710
11i	3-OCH_3-C_6H_4-	1711
11j	4-CH_3-C_6H_4-	1712
11k	3-CH_3-C_6H_4-	1713
11l	3,4-$(Cl)_2$-C_6H_3-	1709

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 2/17/2006 2:13:23 PM
Sample Name : NV-22
Sample ID : NV-22
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-22.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:11.9(Scan#:1397)
MassPeaks:314 BasePeak:247(623473)
RawMode:Single 11.9(1397)
BG Mode:None
intensity



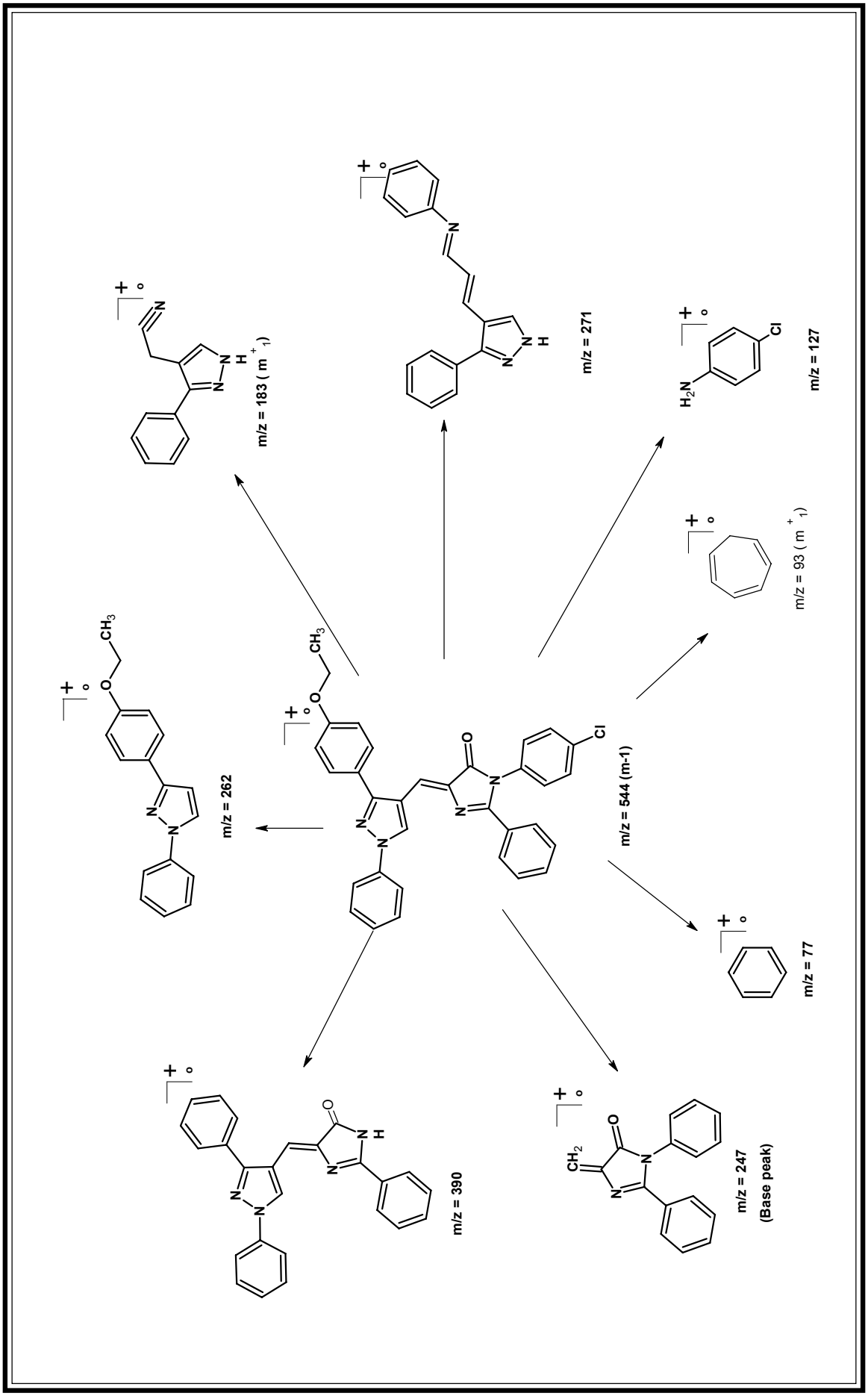
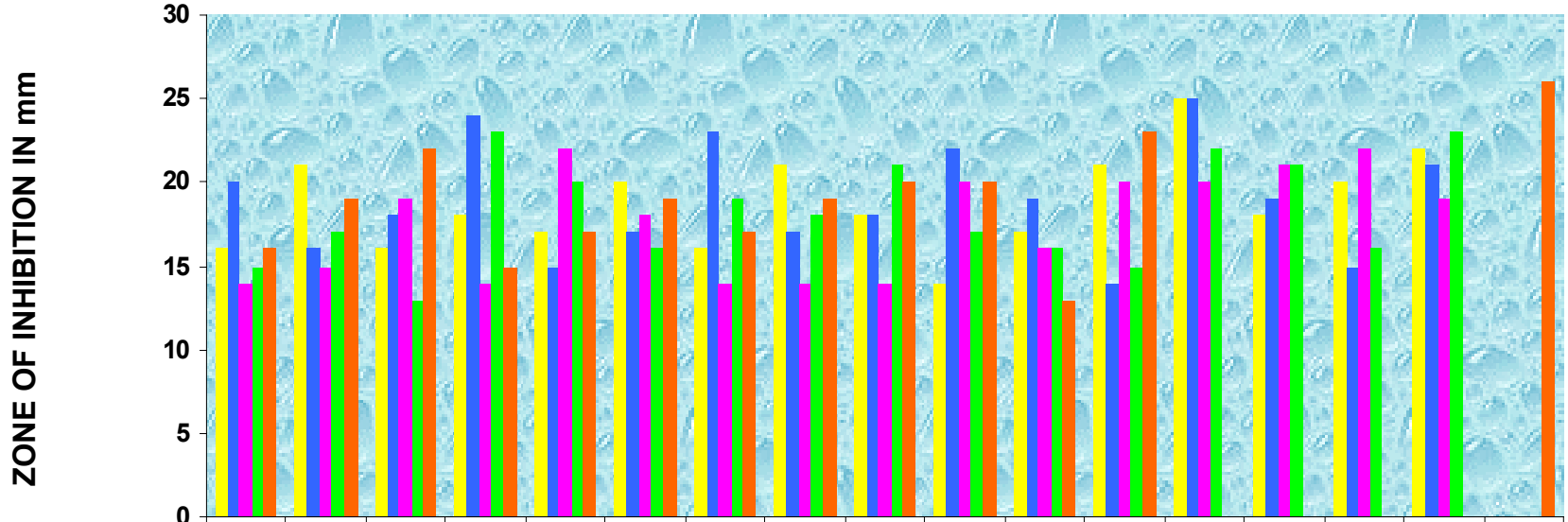

m/z = 544 (m-1)
m/z = 271
m/z = 183 (m+1)
m/z = 127
m/z = 93 (m+1)
m/z = 262
m/z = 77
m/z = 390
m/z = 247
(Base peak)

TABLE-9 : PHYSICAL CONSTANTS OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL 4'-PYRAZOLYL-METHINE)-IMIDAZOLIN-5-ONES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
9a	C_6H_5-	$C_{33}H_{26}N_4O_2$	510	198	0.57	68	10.97	10.92
9b	4-Cl-C_6H_4-	$C_{33}H_{25}ClN_4O_2$	544.5	170	0.49	60	10.28	10.23
9c	3,4-$(Cl)_2$-C_6H_3-	$C_{33}H_{24}Cl_2N_4O_2$	579	148	0.48	79	9.67	9.61
9d	4-Br-C_6H_4-	$C_{33}H_{25}BrN_4O_2$	589	159	0.67	60	9.50	9.45
9e	4-F-C_6H_4-	$C_{33}H_{25}FN_4O_2$	528	118	0.53	53	10.60	10.54
9f	3-Cl,4-F-C_6H_3-	$C_{33}H_{24}ClFN_4O_2$	562.5	221	0.55	58	9.95	9.92
9g	2-OCH_3-C_6H_4-	$C_{34}H_{28}N_4O_3$	540	168	0.49	62	10.36	10.31
9h	4-OCH_3-C_6H_4-	$C_{34}H_{28}N_4O_3$	540	201	0.52	66	10.36	10.33
9i	2-CH_3-C_6H_4-	$C_{34}H_{28}N_4O_2$	524	206	0.60	63	10.68	10.62
9j	4-CH_3-C_6H_4-	$C_{34}H_{28}N_4O_2$	524	156	0.59	72	10.68	10.64
9k	2-NO_2-C_6H_4-	$C_{33}H_{25}N_5O_4$	555	177	0.63	69	12.61	12.57
9l	4-NO_2-C_6H_4-	$C_{33}H_{25}N_5O_4$	555	192	0.49	58	12.61	12.55

*TLC Solvent System : Acetone : Benzene (1.5 : 8.5)

GRAPHICAL CHART NO. 9 : ANTIMICROBIAL ACTIVITY OF 1,N-ARYL-2-PHENYL-4-(1',N-PHENYL-3'-*P*-ETHOXYPHENYL-4'-PYRAZOLYLMETHINE)-IMIDAZOLIN-5-ONES



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	16	21	16	18	17	20	16	21	18	14	17	21	25	18	20	22	0
S. aureus	20	16	18	24	15	17	23	17	18	22	19	14	25	19	15	21	0
E. aerogenes	14	15	19	14	22	18	14	14	14	20	16	20	20	21	22	19	0
P. aeruginosa	15	17	13	23	20	16	19	18	21	17	16	15	22	21	16	23	0
A. niger	16	19	22	15	17	19	17	19	20	20	13	23	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

From the experimental data it has been observed that all the compounds of type (VII) were active against Gram positive and Gram negative bacterial species.

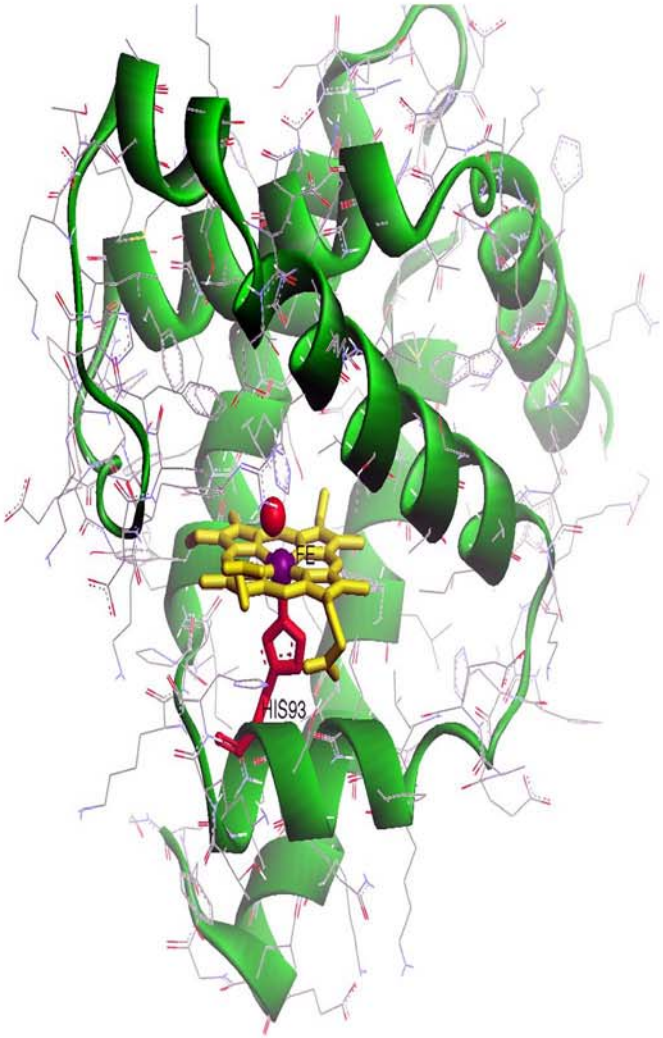
It was observed that the compounds showed good activity against Gram positive bacteria. Maximum activity was observed in compounds having R=4-chloro phenyl, 4-methoxyphenyl and 4-nitrophenyl against ***B.coccus***. The compounds bearing R=4-bromophenyl ,2-methoxyphenyl and 4-tolyl have highly inhibited the growth of ***S.aureus***.

Compounds with R=4-fluorophenyl showed significant activity against ***Aerogenes***. While the compounds bearing R=4-bromophenyl and 2-tolyl have fairly inhibited the growth ***Pseudomonas***.

ANTIFUNGAL ACTIVITY

All the compounds were active against ***A.niger.*** Maximum activity was observed by the compounds bearing R=3,4,-dichlorophenyl and 4-nitrophenyl.

The antibacterial activity was compared with standard drug viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

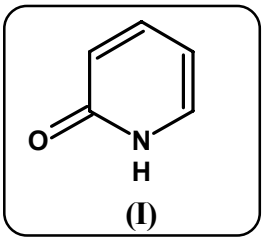


PART-V

STUDIES ON CYANOPYRIDONES

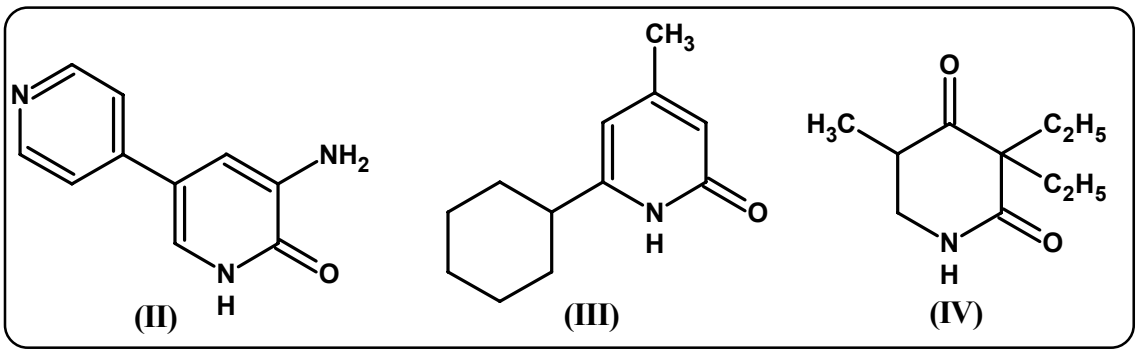
INTRODUCTION

Biosignificant pyridones form a component in a number of useful drugs and are associated with many biological, pharmaceutical and therapeutic activities. Pyridones, with a carbonyl group at position-2 (I) have been subject of extensive study in the recent years. Synthetic pyridone derivatives contribute much to the searchable literature of pyridone derivatives in huge libraries owing to their wide applicability in different fields.



(I)

Some 2-pyridones, which are pharmacologically important are as under: eg. amrinone(II), ciclopirox(III) and methylprylon (IV).

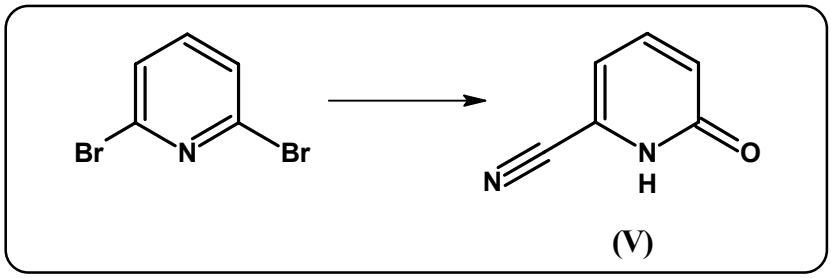


(II) **(III)** **(IV)**

SYNTHETIC ASPECTS

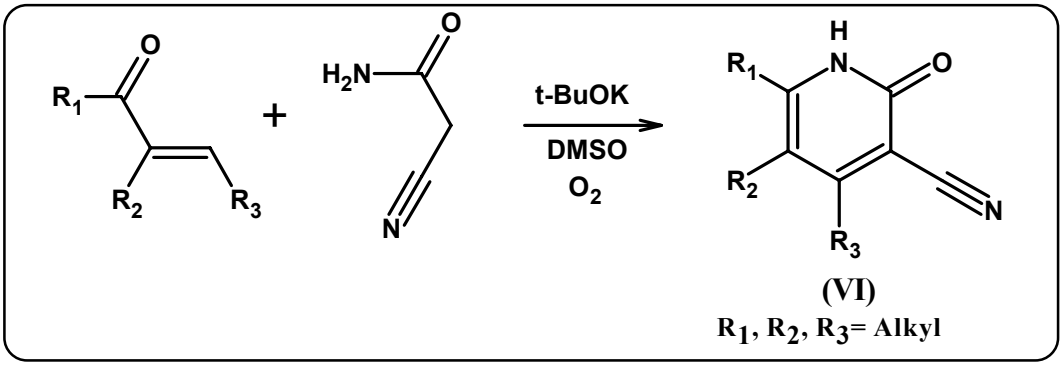
Different methods for the preparation of cyanopyridones are as follows :

1. W. Russel Bowman et. al.[248] have synthesised cyanopyridones from 2,6-dibromopyridine in presence of chlorotrimethylsilane and sodium iodide in acetonitrile.



(V)

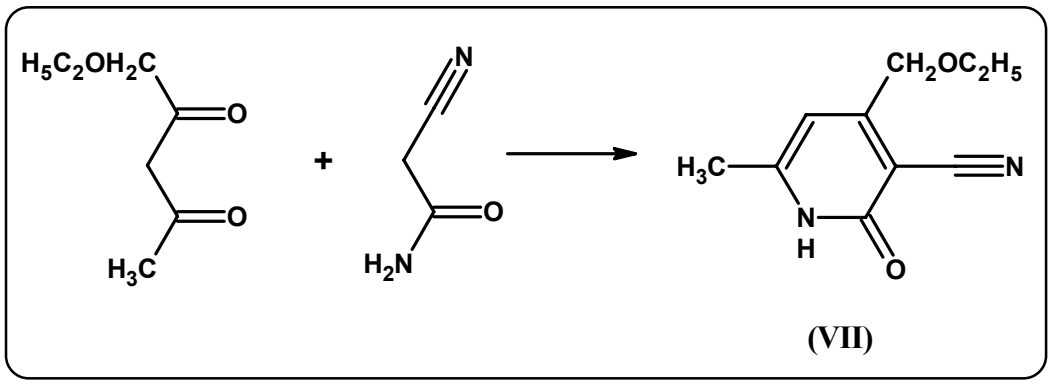
2. Rajul Jain et. al.[249] have synthesised 3-cyano-2-pyridone by the reaction of various enones with cyanoacetamide in presence of *t*-BuOK in DMSO under O_2 atmosphere.



(VI)

R_1, R_2, R_3= Alkyl

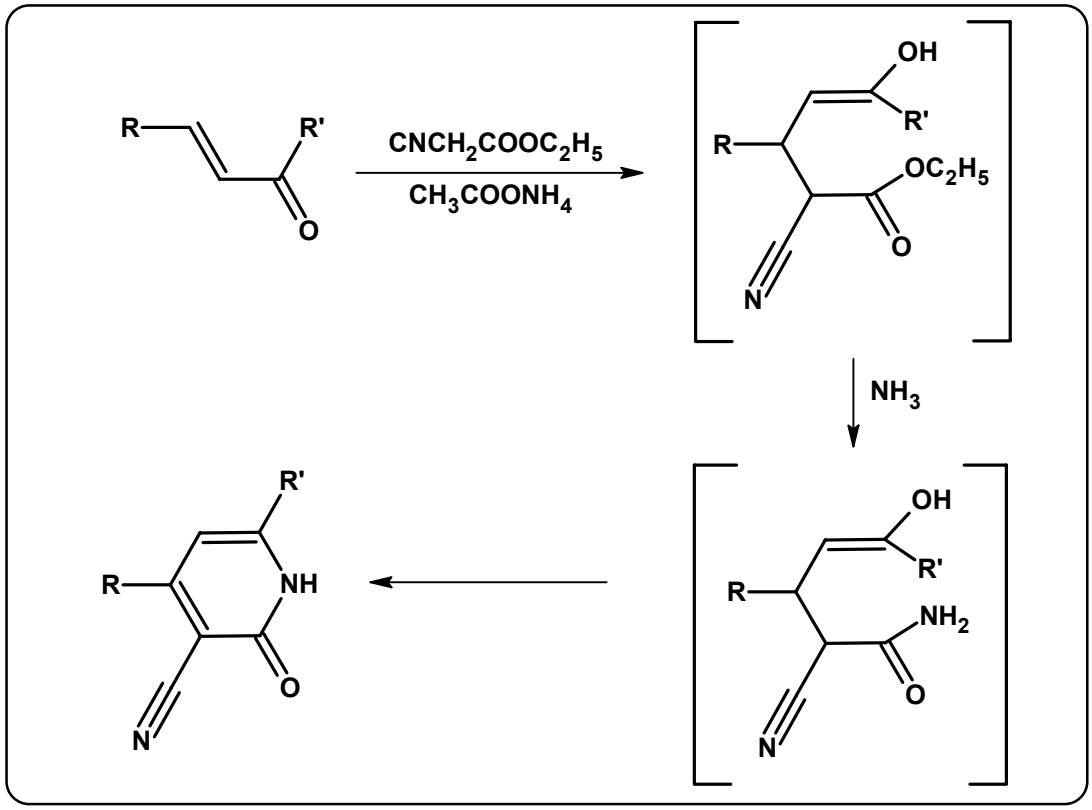
3. K. Follkers and S. A. Harris[250] have synthesised 3-cyano-2-pyridone by the condensation of cyanoacetamide with 1,3-diketone or 3-ketoester.



(VII)

MECHANISM

The addition reaction between ethylcyano acetale and a, b-unsaturated ketone yield cyanopyridone via Michael addition. Here, a, b-unsaturated compound is known as acceptor and active methylene group containing compound is known as addender. It involves nucleophillic addition of carbanion to the C=C of the acceptor.



THERAPEUTIC IMPORTANCE

Pyridone derivatives have been found to possess variety of therapeutic activities as shown below.

(a) Anticancer[251]

(b) Herbicidal[252]

(c) Pesticidal[253,254]

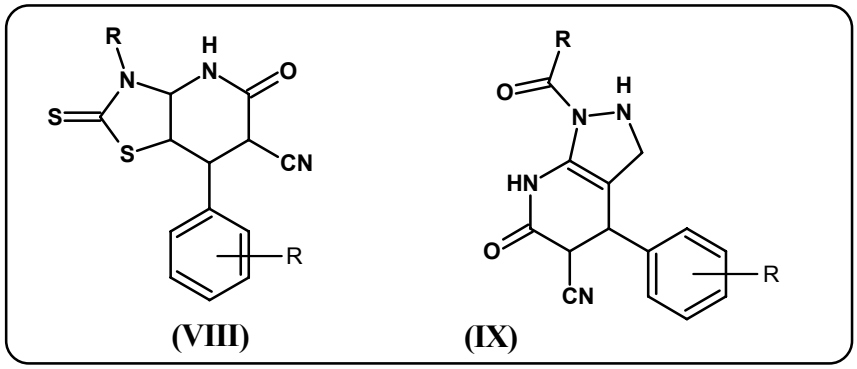
(d) Antimicrobial[255]

(e) Angitensin II antagonist[256-258]

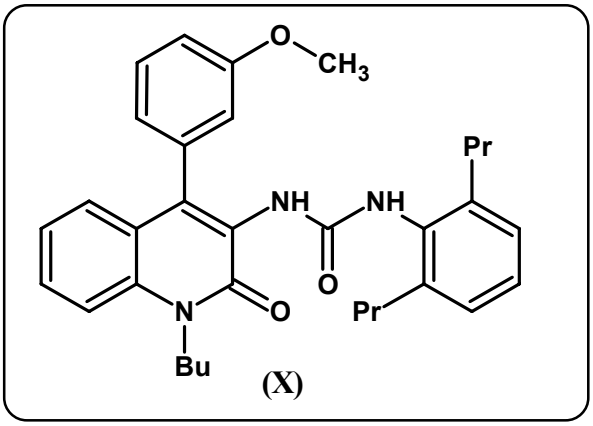
(f) Antiviral[259]

(g) AntiHIV[260]

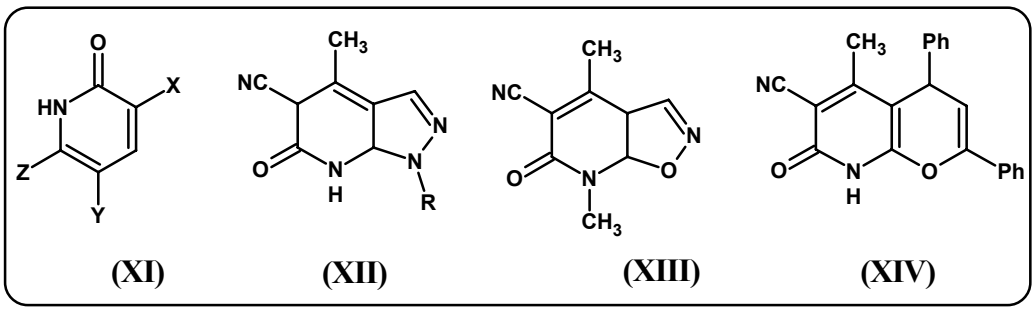
Peter and co-workers[261] have described pyridinylmethyl substituted pyridines and pyridones as angitensin II antagonist. H. Posnes[262] have synthesized 2-pyridones and 2-pyrones as physiologically active compounds. Mukhtar Hussain Khan and co-workers[263,264] have prepared 2-pyridone derivatives (VIII) and (IX) which possess insecticidal and pesticidal activity.



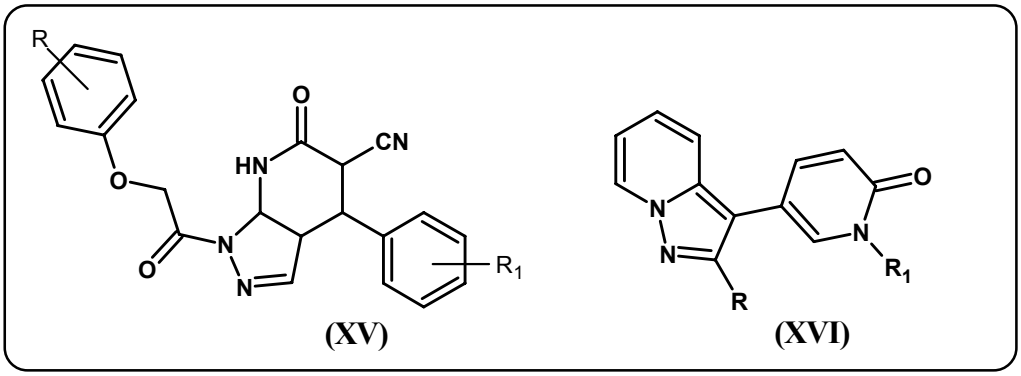
Morishita Koji et al.[265] have synthesized *m*-(2-oxo-l,2-dihydropyridyl) urea derivatives (X) possessing cholesterol acyltransterase (ACAT) inhibitory activity and are useful for the treatment of hyperlipidemia and arteriosclerosis.



Collins et al.[266] have prepared heteroaryl pyridones as GABA a,b ligands (XI). Pedneker[267] have synthesized fused 2-pyridone derivatives (XII), (XIII) and (XIV) as useful heterocyclic moieties as they possess broad spectrum of biological activities such as antiviral, CNS depressant, bactericidal and ulcer inhibitor.



E. Amer[268] prepared 3-cyano-2-pyridone derivatives displaying significant antimicrobial activity. Abou El-Fotooh and co-workers[269]. have demonstrated pyridones as anticancer agent. M. G. Nizamuddin et al.[270] have prepared cyanopyridone derivatives (XV) and documented their antifungal activity. Tanaka Akira et al.[271] have prepared pyrazolo pyridone derivatives (XVI).



Xi Qi et. al.[272] have investigated cyanopyridones useful as phosphatase inhibitors and studied their biological activities. Darcq Michael. G. et. al.[273] have discovered some new cyanopyridone derivatives which showed *in vitro* HCV NS5B inhibitory activity and exhibited IC_{50} in the range of 0.0001 μM to 100 μM. Their pharmaceutical compositions are useful for treating HCV infections. Isobe Y. et. al.[274] have prepared pyrimidine diones and evaluated them as antiallergic agents. Nersesyan K. et. al.[275] have investigated some new cyanopyridones possessing genotoxic activity in murine cells and antitumor activity.

Recently, Devdas B. et. al.[276] have synthesised pyridone derivatives which are useful for treating diseases and conditions caused or exacerbated by unregulated P38 MAP kinase and/or TNF activity, such as inflammation, ischemia, viral infections and autoimmune diseases. Wang S. and co-workers[277] have prepared 2-pyridones containing tricyclic alkaloid derivatives as potential inhibitors of tumor cell proliferation by regioselective intramolecular N- and C-acylation of 2-pyridone. A novel series of pyridone inhibitors has been identified through pharmacophore analysis as potent and selective VLA-4 integrin antagonists by Jason Witherington et. al.[278] Jiang Q. and co-workers[279] have identified a series of novel pyridones as kinase inhibitors of ALK.

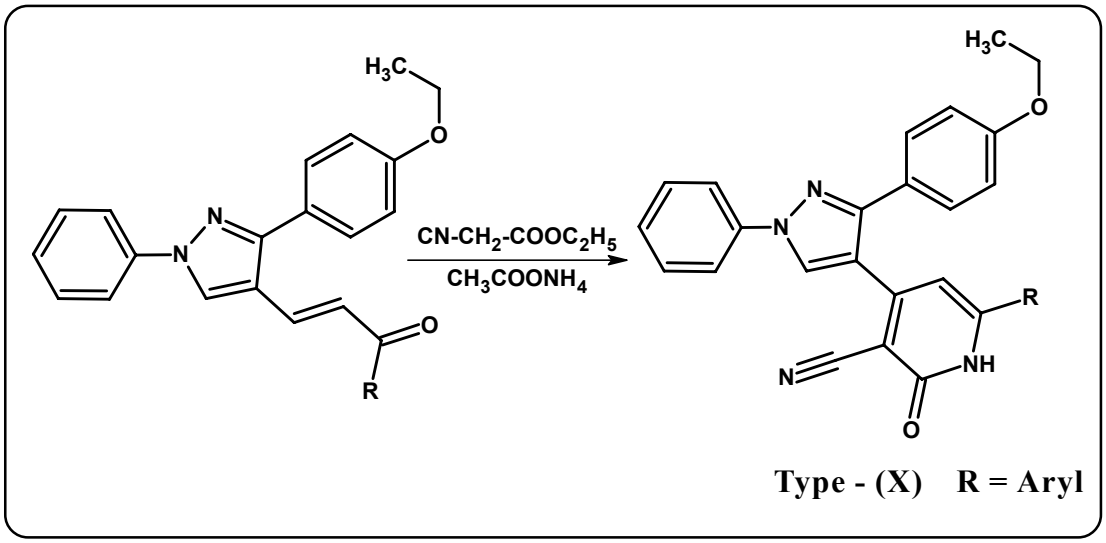
Thus the important role played by cyanopyridone nucleus for various physiological activities prompted us to explore cyanopyridone chemistry by synthesing its derivatives bearing pyrazole ring system of therapeutic importance, in order to achieving compounds having better drug potential which has been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

Pyridone derivatives have remarkable therapeutic activity. Taking this into consideration, we have undertaken the preparation of pyridone derivatives by the condensation of chalcones of type-(I) with ethylcyanoacetate in the presence of ammonium acetate as shown under.

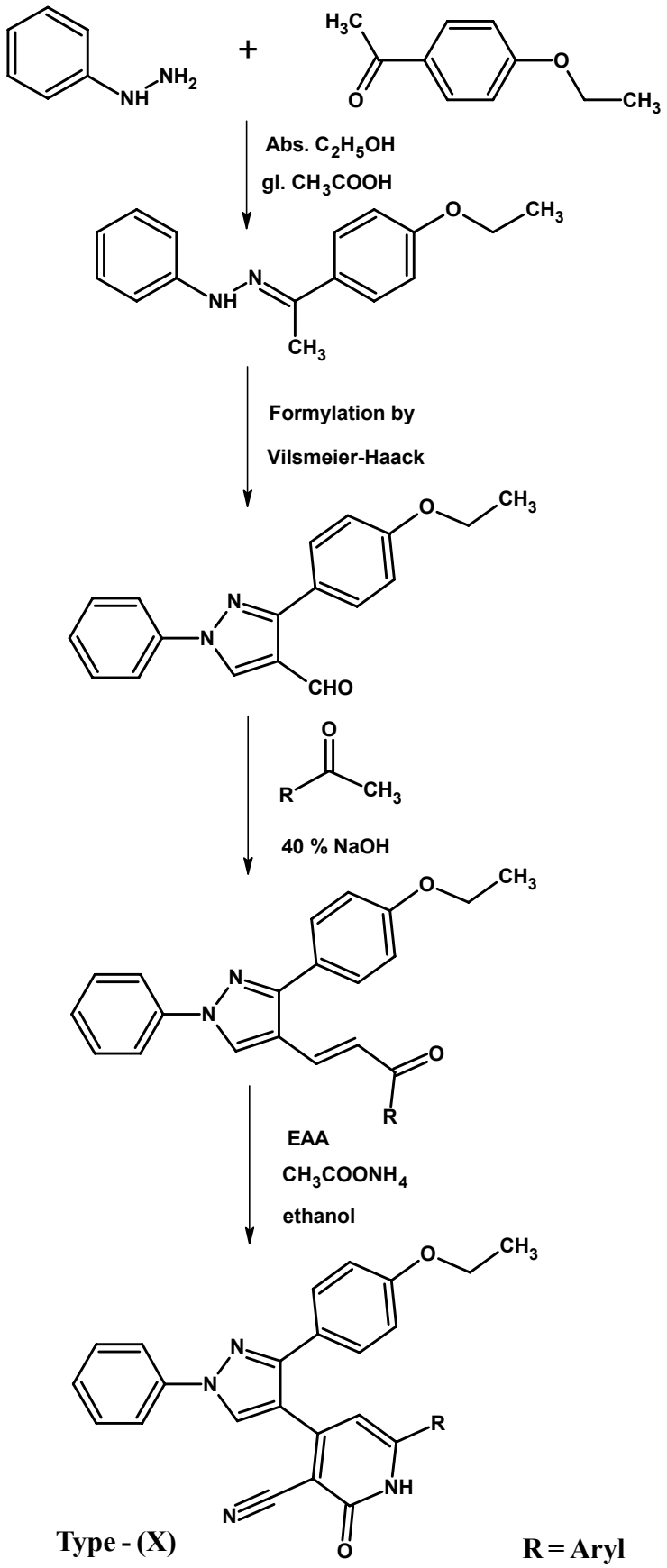


Type - (X) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography. .

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (X) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

See [A] Part-I, Section-I (C).

(D) Synthesis of 3-Cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-6-(*p*-bromophenyl)-1,2-dihydro-2-pyridone

A mixture of 1-(*p*-bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.87 g, 0.01 M), ethylcyanoacetate (1.13 g, 0.01 M) and ammonium acetate (6.16 g, 0.08 M) in absolute alcohol was refluxed for 12 hrs. The reaction mixture was poured on to crushed ice and product was isolated and crystallised from ethanol. Yield 68%, m.p. 198^{o}C ($C_{29}H_{21}BrN_4O_2$; Required : C, 64.81; H, 3.94; N, 10.43; Found : C, 64.75; H, 3.90; N, 10.39%).

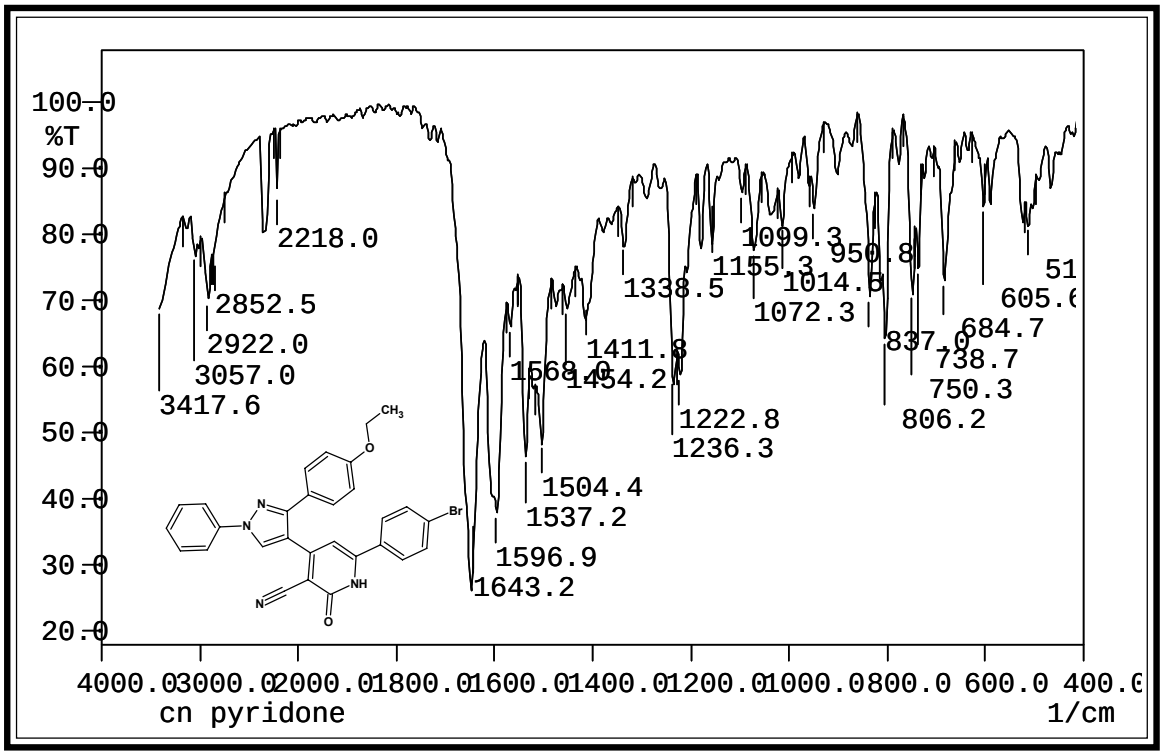
TLC solvent system : Acetone : Benzene (3 : 7).

Similarly other substituted pyridones have been prepared. The physical data are recorded in Table No. 10.

(E) Antimicrobial activity of 3-Cyano-4-(1',N-phenyl-3'-*o*-ethoxyphenyl-pyrazol-4'-yl)-6-aryl-1,2-dihydro-2-pyridones

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.10.

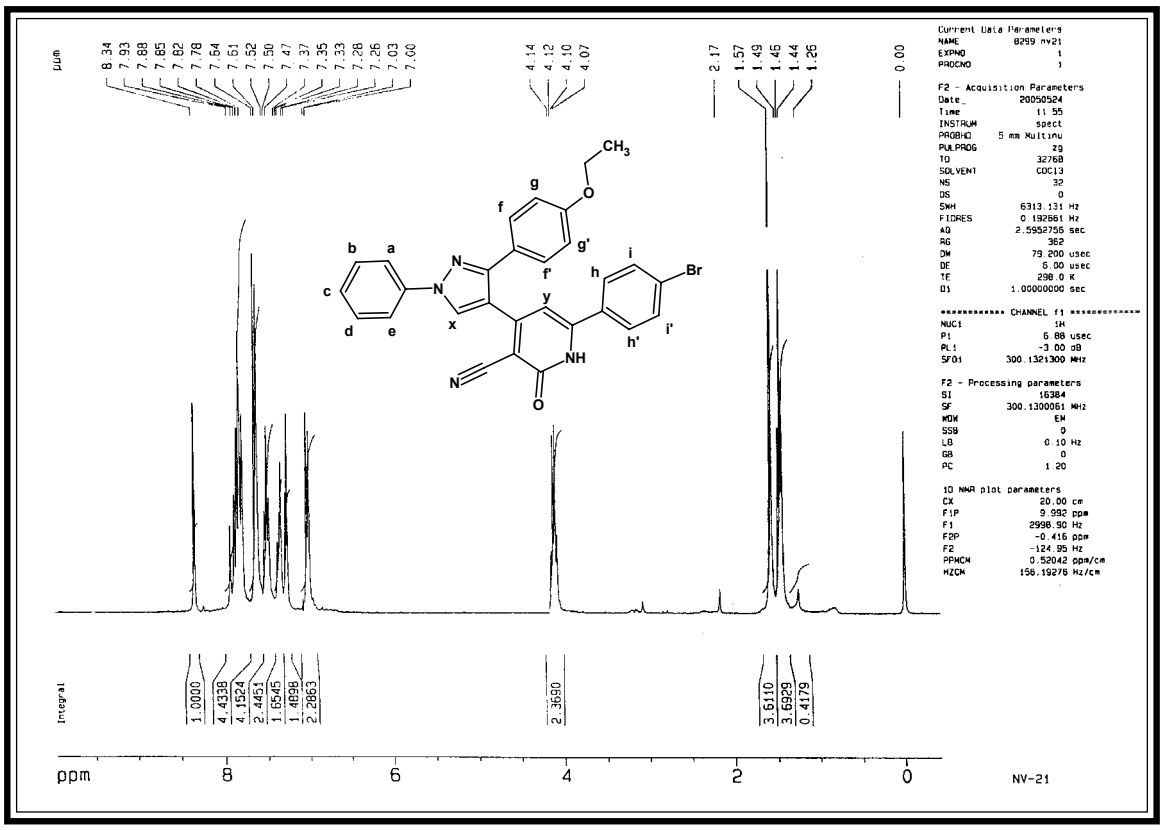
IR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-(*p*-BROMOPHENYL)-1,2-DIHYDRO-2-PYRIDONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2922	2975-2950	413
$-CH_3$	C-H str. (sym.)	2852	2880-2860	
	C-H i.p.def. (asym.)	1454	1470-1435	
Aromatic	C=C str.	1537	1585-1480	414
	C-H i.p. def.	1099	1125-1090	
	C-H o.o.p. def.	837	835-810	
Pyrazole	C=N str.	1596	1630-1590	415
moiety	C-N str.	1155	1230-1020	
Ether	C-O-C str. (asym.)	1236	1275-1200	413
	C-O-C str. (sym.)	1072	1075-1020	
Pyridone ring	C^{O}N str.	2218	2240-2120	413
	C=O str.	1643	1760-1655	
	N-H str.	3423	3450-3250	
	N-H def.	1596 (overlapped)	1650-1580	
Halide	C-Br str.	750	600-800	420

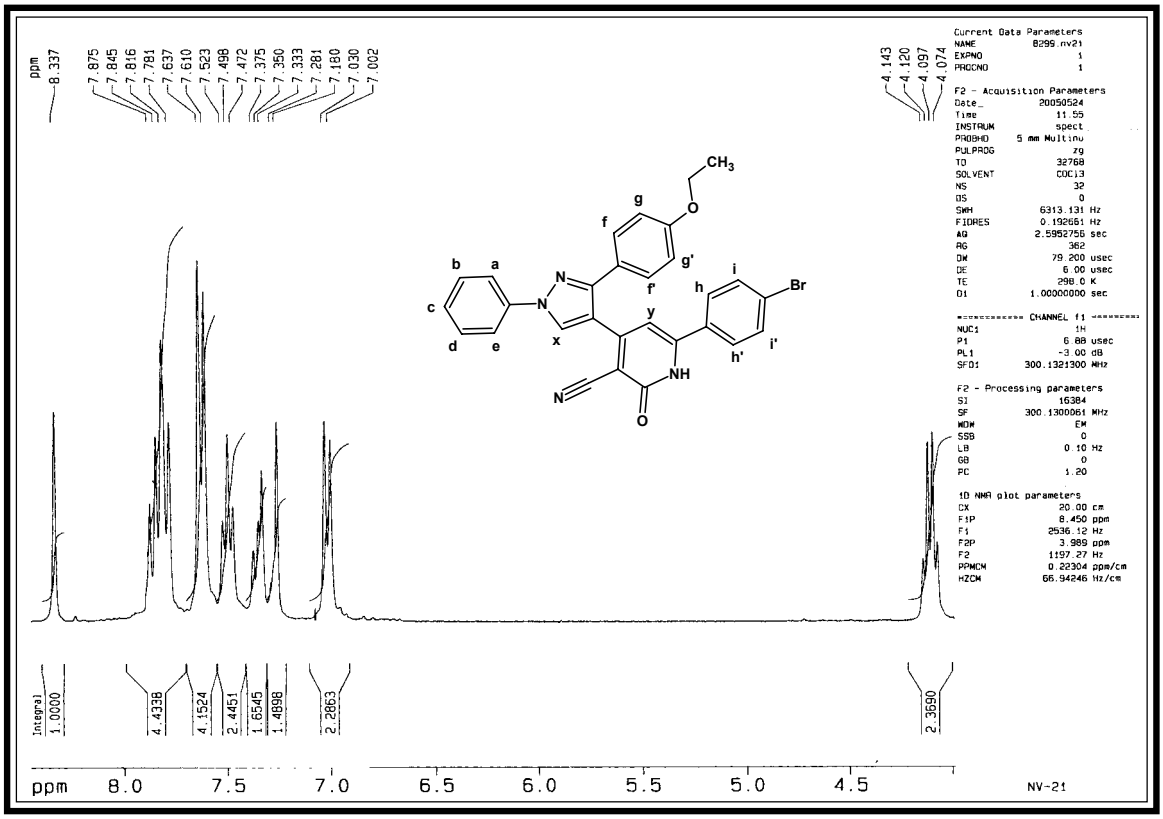
PMR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-(*p*-BROMOPHENYL)-1,2-DIHYDRO-2-PYRIDONE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.26-1.49	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.0
2.	4.07-4.14	2H	quartret	$-O\underline{CH}_2CH_3$	J_{CH_2}=6.0
4.	7.002-7.030	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.4
3.	7.28	1H	singlet	CH_y	-
5.	7.33-7.37	1H	triplet	Ar-H_c	-
6.	7.47-7.52	2H	triplet	Ar-H_{bd}	-
7.	7.61-7.63	4H	doublet	Ar-$H_{ff'}$,Ar-$H_{hh'}$	J_{fg}=8.4
8.	7.78-7.87	4H	multiplet	Ar-$H_{a,e}$, Ar-$H_{ii'}$	-
9.	8.33	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION



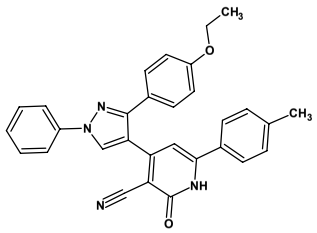
IR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-(*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Sr. No.	R	C=O str.	C^{O}N str.
4a	C_6H_5-	1650	2217
4b	4-NH_2-C_6H_4-	1649	2225
4c	4-Cl-C_6H_4-	1643	2219
4d	4-Br-C_6H_4-	1643	2218
4e	4-F-C_6H_4-	1654	2218
4f	2-OH-C_6H_4-	1643	2214
4g	4-OH-C_6H_4-	1649	2219
4h	4-OCH_3-C_6H_4-	1646	2212
4i	4-CH_3-C_6H_4-	1642	2220
4j	3-NO_2-C_6H_4-	1659	2214
4k	4-NO_2-C_6H_4-	1637	2218
4l	2-C_4H_3-	1637	2220

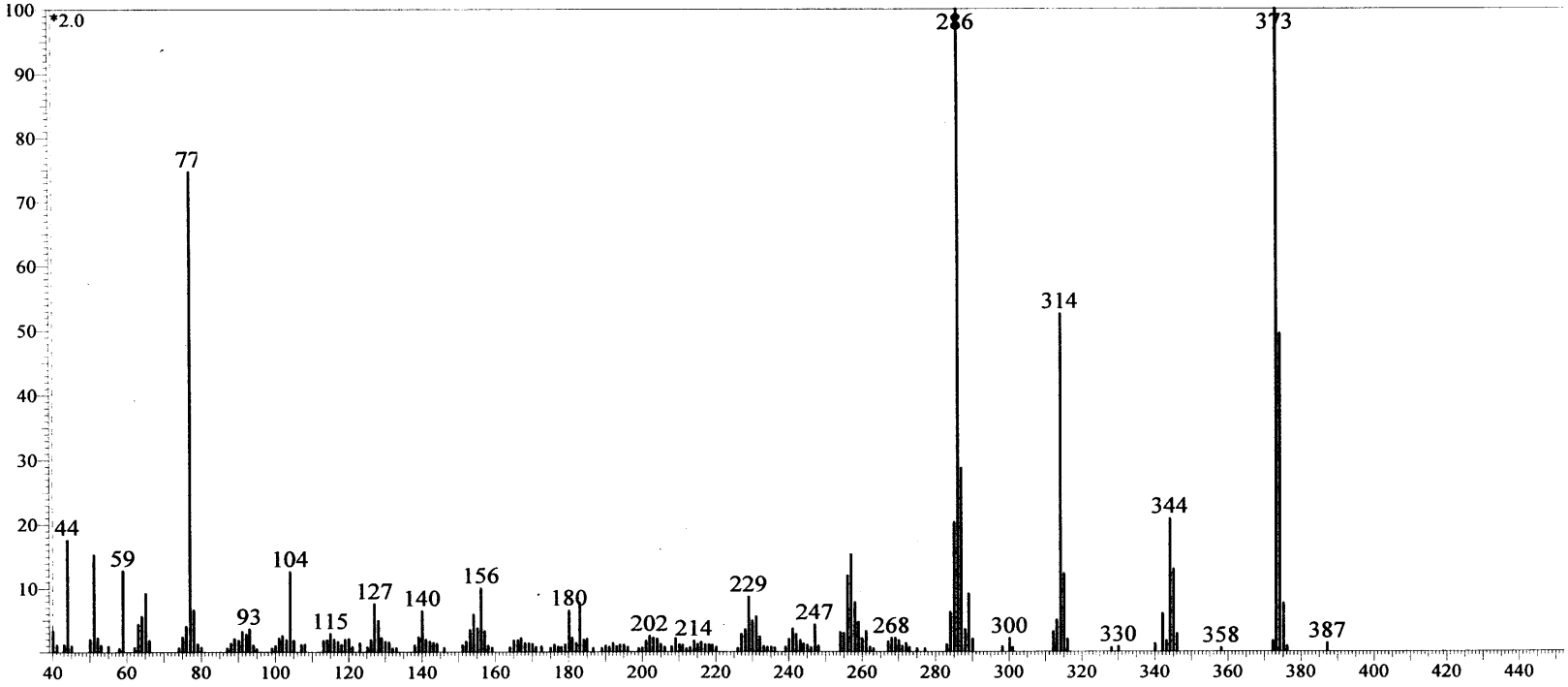
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information



Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 2/28/2006 12:22:29 PM
Sample Name : NV-24
Sample ID : NV-24
Data File : C:\GCMSsolution\Data\H.H.PAREKH\NV-24.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:5.9(Scan#:678)
MassPeaks:203 BasePeak:373(424007)
RawMode:Single 5.9(678)
BG Mode:None
intensity



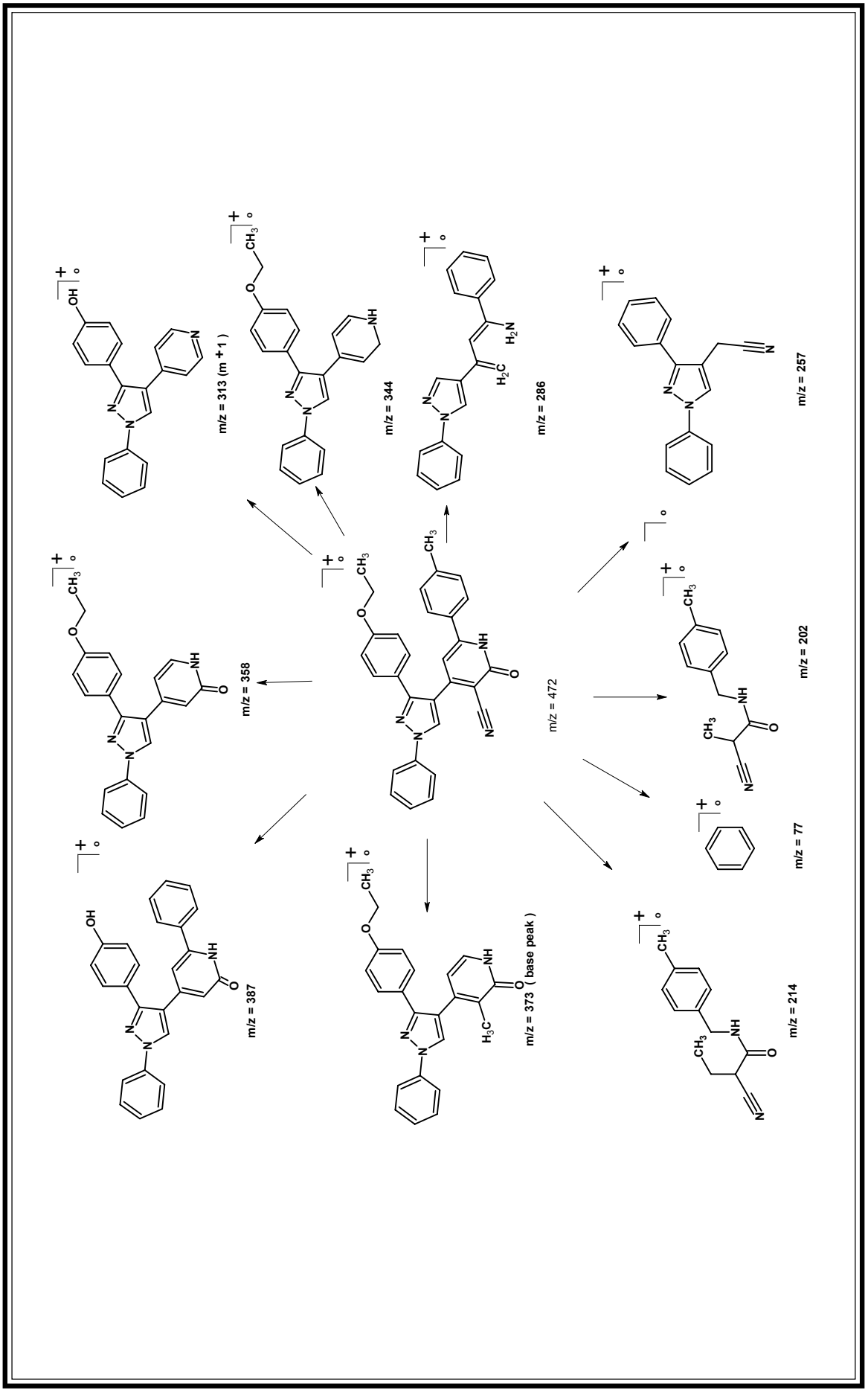
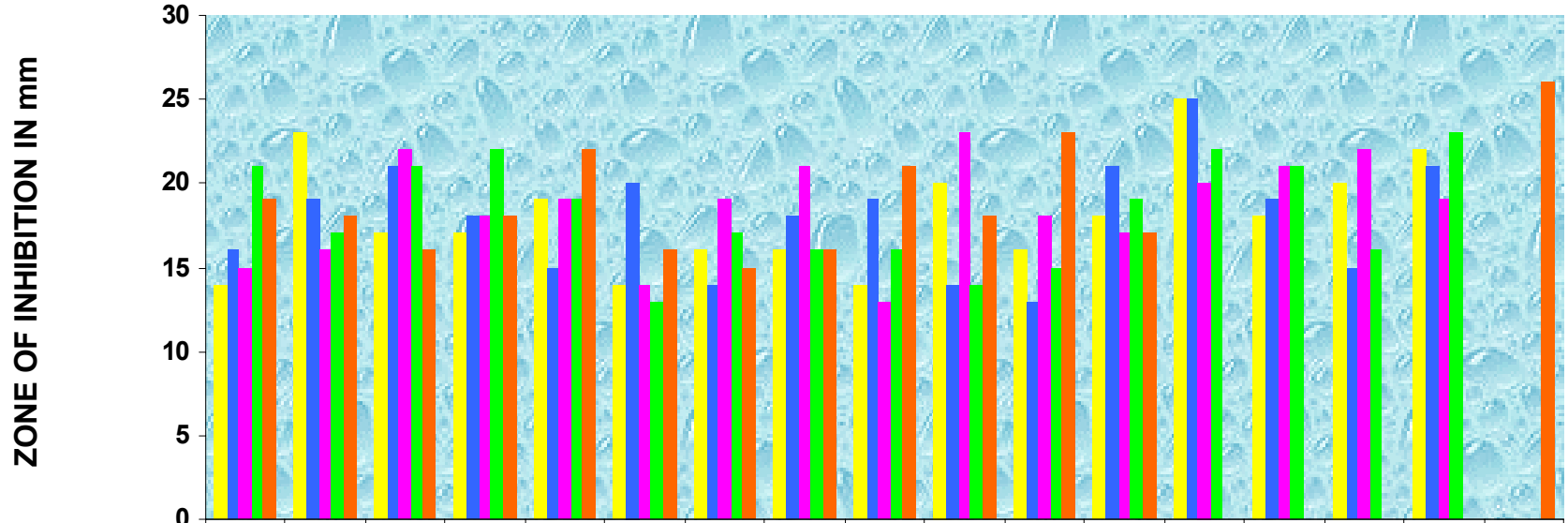

m/z = 472
m/z = 313 (m +1)
m/z = 344
m/z = 286
m/z = 257
m/z = 358
m/z = 202
m/z = 387
m/z = 373 (base peak)
m/z = 77
m/z = 214

TABLE-10: PHYSICAL CONSTANTS OF 3-CYANO-4-(1',N-PHENYL-3'-*P*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6- ARYL-1,2-DIHYDRO-2-PYRIDONES.

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
10a	C_6H_5-	$C_{28}H_{26}N_4O_2$	458	190	0.59	68	12.22	12.17
10b	4-NH_2-C_6H_4-	$C_{29}H_{22}N_4O_2$	473	215	0.53	59	14.79	14.73
10c	4-Cl-C_6H_4-	$C_{29}H_{21}ClN_4O_2$	492.5	260	0.49	63	11.37	11.33
10d	4-Br-C_6H_4-	$C_{29}H_{21}BrN_4O_2$	537	198	0.62	68	10.43	10.39
10e	4-F-C_6H_4-	$C_{29}H_{21}FN_4O_2$	476	235	0.63	63	11.76	11.71
10f	2-OH-C_6H_4-	$C_{29}H_{22}N_4O_3$	474	230	0.53	72	11.81	11.75
10g	4-OH-C_6H_4-	$C_{29}H_{22}N_4O_3$	474	177	0.59	80	11.81	11.77
10h	4-OCH_3-C_6H_4-	$C_{30}H_{24}N_4O_3$	488	157	0.53	59	11.47	11.42
10i	4-CH_3-C_6H_4-	$C_{30}H_{24}N_4O_2$	472	225	0.48	70	11.86	11.83
10j	3-NO_2-C_6H_4-	$C_{29}H_{21}N_5O_4$	503	203	0.56	56	13.91	13.87
10k	4-NO_2-C_6H_4-	$C_{29}H_{21}N_5O_4$	503	156	0.63	69	13.91	13.85
10l	2-C_4H_3S-	$C_{27}H_{20}N_4O_2S$	464	157	0.48	72	12.06	12.01

*TLC Solvent System : Acetone : Benzene (3 : 7)

GRAPHICAL CHART NO. 10 : ANTIMICROBIAL ACTIVITY OF 3-CYANO-4-(1',N-PHENYL-3'-*P*- ETHOXY- PHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	14	23	17	17	19	14	16	16	14	20	16	18	25	18	20	22	0
S. aureus	16	19	21	18	15	20	14	18	19	14	13	21	25	19	15	21	0
E. aerogenes	15	16	22	18	19	14	19	21	13	23	18	17	20	21	22	19	0
P. aeruginosa	21	17	21	22	19	13	17	16	16	14	15	19	22	21	16	23	0
A. niger	19	18	16	18	22	16	15	16	21	18	23	17	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

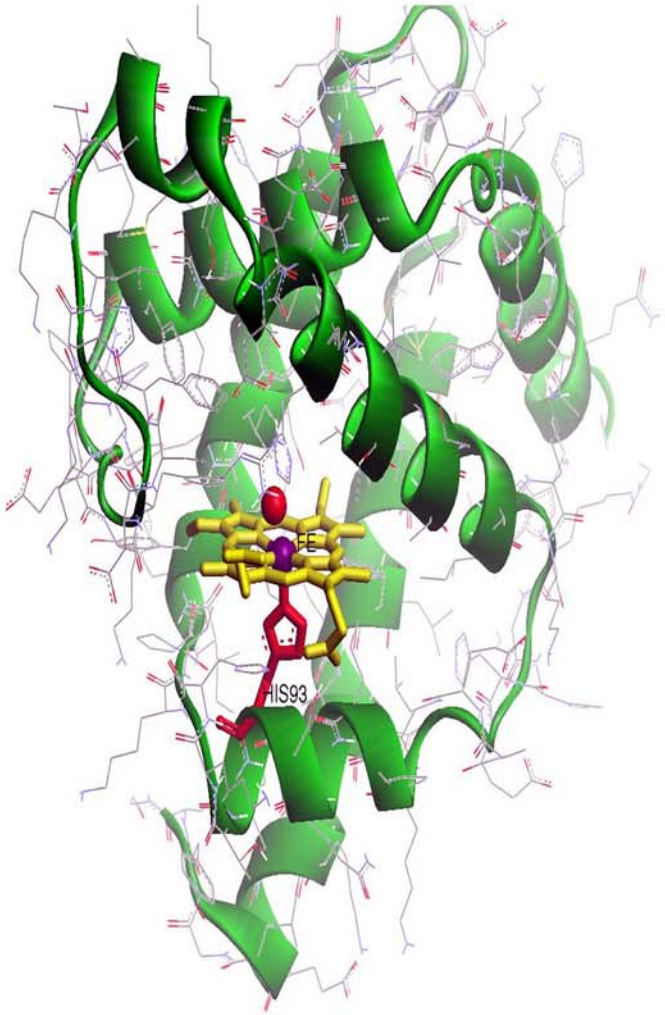
From the experimental data it has been concluded that all the compounds were mildly active against Gram positive bacterial strains except R=4-chlorophenyl,4-aminophenyl which showed highest activity against ***B.coccus*** and R=2-thienyl which showed highest activity against ***S.aureus***.

In case of Gram negative bacterial strains, the compounds bearing R=4-chlorophenyl, 4-methoxyphenyl and 3-nitrophenyl have exhibited significant activity against ***Aerogenes.*** The compounds bearing R=phenyl, 4-chlorophenyl and 4-bromophenyl have shown maximum activity against ***Pseudomonas***.

ANTIFUNGAL ACTIVITY

All the compounds were mildly active against ***A.niger.*** Maximum activity was shown by the compounds bearing R=4-fluorophenyl, 4-tolyl and 4-nitrophenyl.

The antibacterial activity was compared with standard drug viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.



PART-VI

STUDIES ON CYANOPYRIDINES

INTRODUCTION

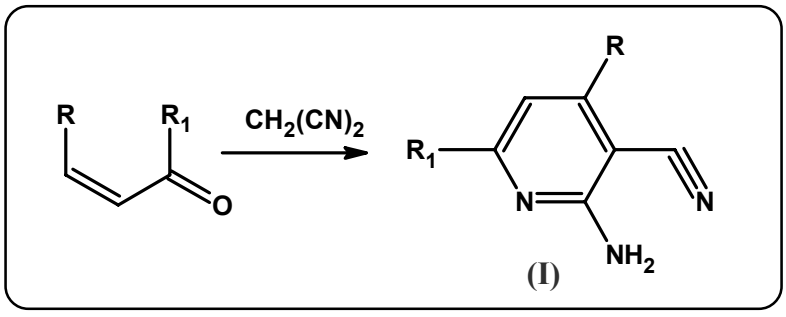
Pyridine is the parent of the series of compounds that is important in pharmaceutical, agriculture and industrial chemistry. Among a wide range of 3-cyanopyridines acquired a special attention due to their wide range of therapeutic activities. Most derivatives are prepared by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry. However the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials.

The pyridine nucleous is found in a large number of commonly used drugs which have diverse pharmacological activities. Interest in the synthesis of multicyclic pyridine containing compounds have increased in recent years because of their biological and pharmacological activities.

SYNTHETIC ASPECTS

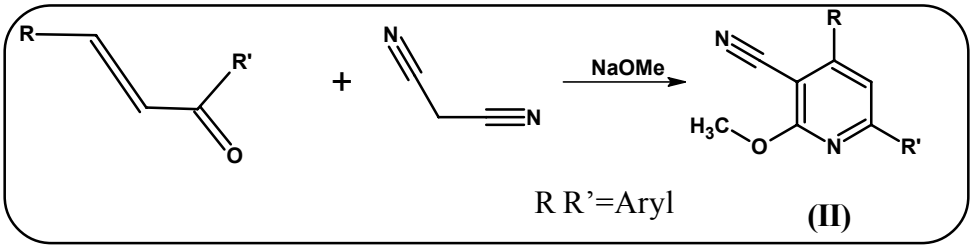
Different method for the preparation of 3-cyanopyridines are available in literature.[280-284] The well known methods are:

1. Sakurai and Midorikaw[285], have reported that malononitrile reacts with a,b-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines(I).



(I)

2. Samour and co-workers prepared substituted cyanopyridines by the condensation of chalcones with ethyl acetoacetate and malononitrile in the presence of ammonium acetate.[286]
3. Amalia Ubeda and co-workers prepared 2-amino-3-cyanopyridine derivatives using arylidene malononitrile + lithium isopropyl amide and DMF dichloride.[287]
4. Dao-Lin& Kimiaki[288] have prepared 2-methoxy-3-cyanopyridine derivatives by the condensation of chalcones with malononitrile in sodium methoxide.



THERAPEUTIC IMPORTANCE

Cyanopyridines have attracted considerable attention as they appeared of interest to possess antibacterial, anticholestermic, antifungal, antihypertensive and antidiabetic activities. Few of them reported are shown below.

(a) Analgesic[289]

(b) Insecticidal[290]

(c) Antisoriasis[291]

(d) AntiHIV[292]

(e) Antifungal[293]

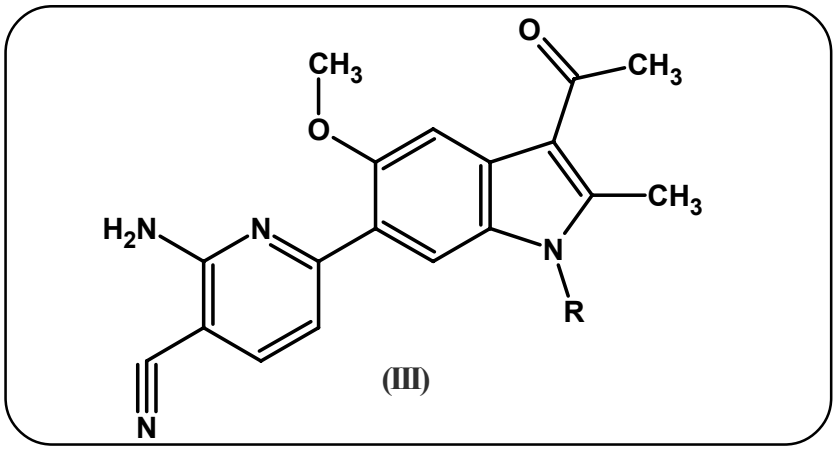
(f) Antiepileptic[294]

(g) Antibacterial[295]

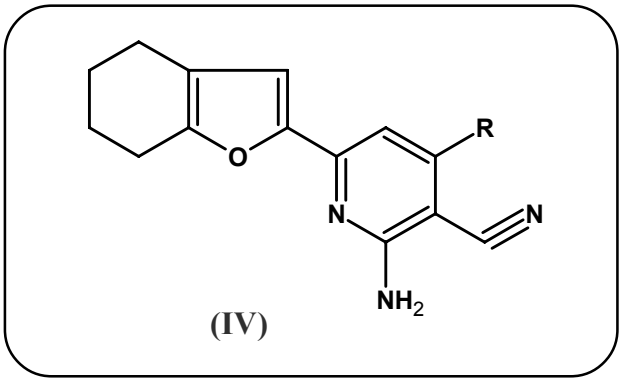
(h) Anticonvulsant[296]

Hussan M. and co-workers[297] have prepared 3-cyanopyridines and reported their pharmacological activity.U. Teu and co-workers[298] have shown cyanopyridines as agrochemical fungicides. H. Yoshida et al.[299] have studied the antihistamic and antiallergic activity of 3-cyanopyridine derivatives.

Gadaginamath and co-workers[300] have synthesized various cyanopyridyl derivatives (III) and documented their variety of biological activities.

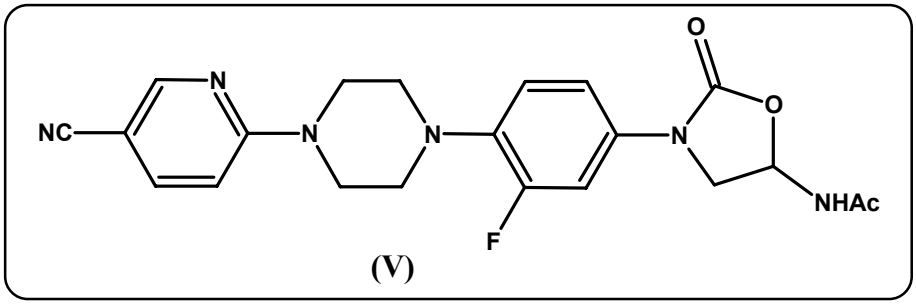


M. Bernard et al.[301] have reported anticonvulsant activity of 3-cyanopyridines. D. G. Bhatt et al.[302] have prepared 3-cyanopyridines as an immunosuppressive agent.S. Guru et al.[303] have synthesized various cyanopyridyl derivatives (IV) and documented their multiple biological activities.



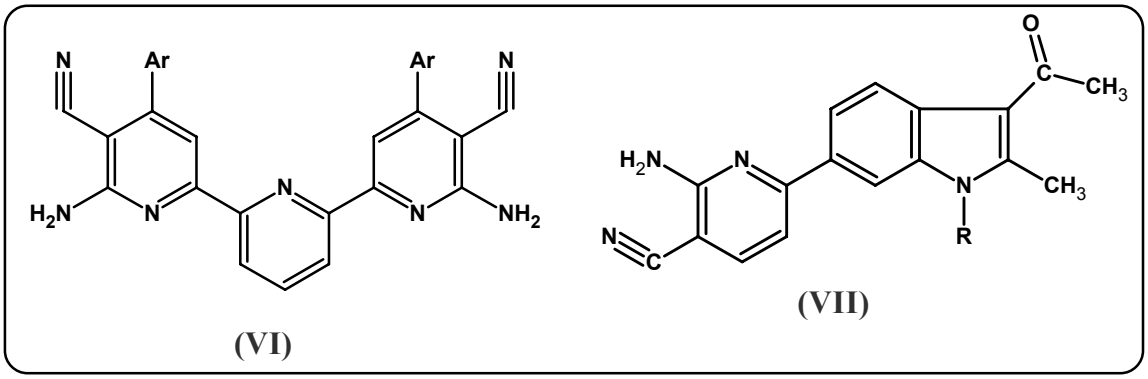
(IV)

John A. Tucker et al.[304] have synthesized novel piperazinyl oxazolidinone containing cyanopyridine (V) as an antibacterial agent.



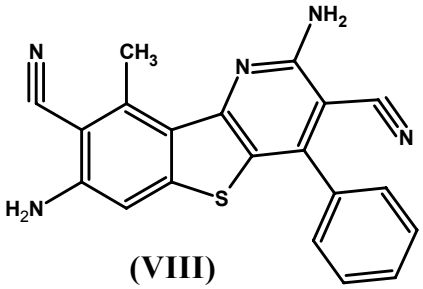
(V)

Manna Fedele and co-workers[305] have reported the antiinflammatory activity of 3-cyanopyridines.Hammana Abou and co-workers[306] have studied anticancer and anti-HIV activity of 3-cyanopyridines. Abdallah Navine et al.[307] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. Abd El-Galil and co-workers[308] have prepared 3-cyanopyridines (VI) and studied their pharmacological activity.El-Nabawia et al.[309] have prepared 2-amino-3-cyano pyridine derivatives (VII) and studied their antimicrobial activity.

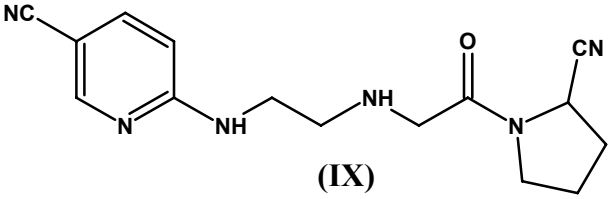


(VI) (VII)

S. V. Roman et al.[310] have synthesized 2-amino-3-cyanopyridines and reported their biological activity. El-Taweel and co-workers[311] have prepared cyanopyridine derivatives and showed their significant biological activity.Pyachenko U. D. et al.[312] have synthesized some cyanopyridines which are useful in the treatment of retroviral disease.Abu and co-workers[313] have prepared novel fused cyanopyridines (VIII) for the treatment and preparation of systemic fungal infection.



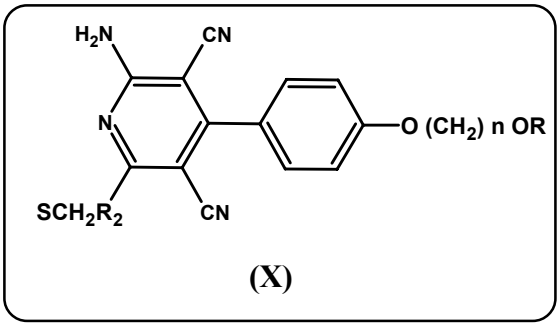
(VIII)



(IX)

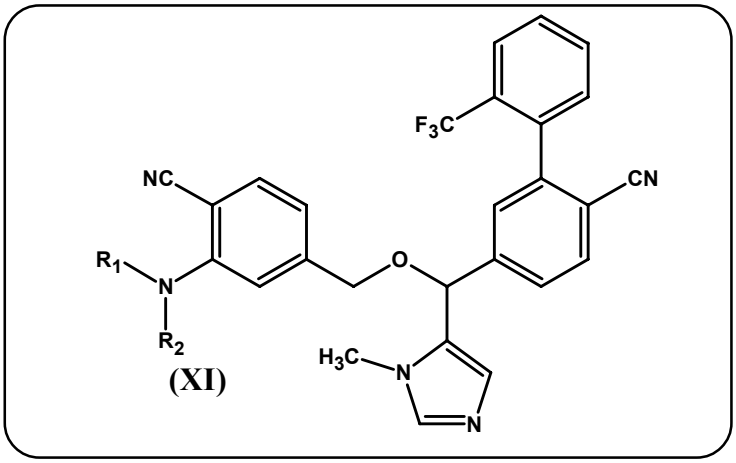
Dipeptidyl peptidase (DPP-IV) inhibition has the potential to become a valuable therapy for diabetes.Marco J. L. et al.[314] have synthesized acetylcholinesterase inhibitors.Edwin B. Villhauer and co-workers[315] have reported the first use of solid-phase synthesis in the discovery of a new DPP-IV inhibitor class and a solution-phase synthesis that is practical up to the multikilogram scale. One compound, NVP-DPP728 (X), is profiled as a potent, selective and shortacting DPP-IV inhibitor that has excellent oral bioavailability and potent antihyperglycemic activity.

Rosentreter Ulrich et al.[316] have synthesized a new cyanopyridine as receptor agonists in the treatment of cardiac or urogenital disease cancer, inflammation, neurodegenerative disease(XI).Moustafa M. A. et al.[317] have prepared cyanopyridne derivatives and reported as antibacterial agents.



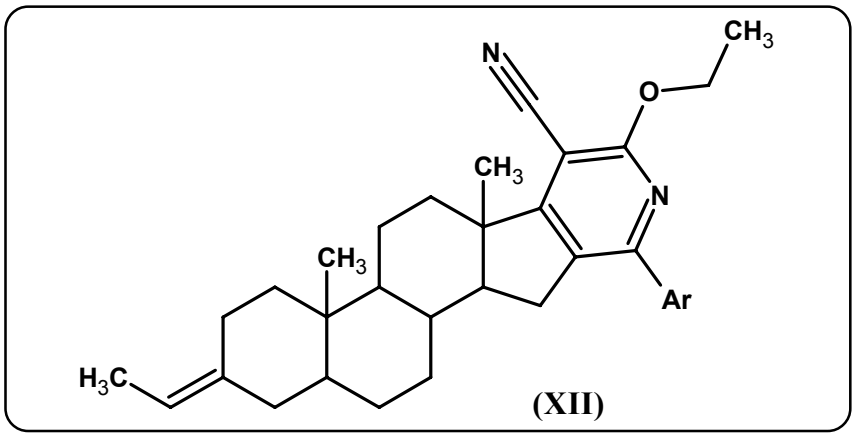
(X)

Recently Eduardo H. S. Sousa et al.[318] documented thionicotinamide coordinated to the a model system for the *in vitro* activation of thioamides antituberculosis drugs.Gary T. Wang and co-workers[319] have synthesized of o-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles as inhibitors of farnesyl transferase(XI)



(XI)

Abdel-Galil E,Amr and Mohamed M. Abdulla[320] have synthesized heterocyclic pyridine derivatives (XII) fused with steroidal structure.



(XII)

In view of therapeutic activities shown by cyanopyridines, it was contemplated to synthesize some new cyanopyridines in search of agents possessing higher biological activity with least side effect have been described as under.

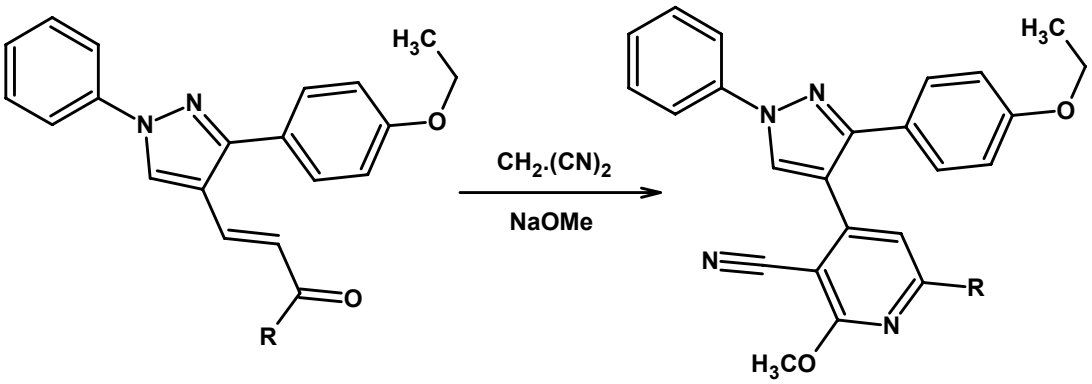
SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-ARYL PYRIDINES

The pyridine nucleus is found in a large number of commonly used drugs which have diverse pharmacological activities. To achieving better drug potency cyanopyridine derivatives of type (XI) have been prepared by the condensation of chalcones of type (I) with malononitrile in the presence of sodium methoxide.

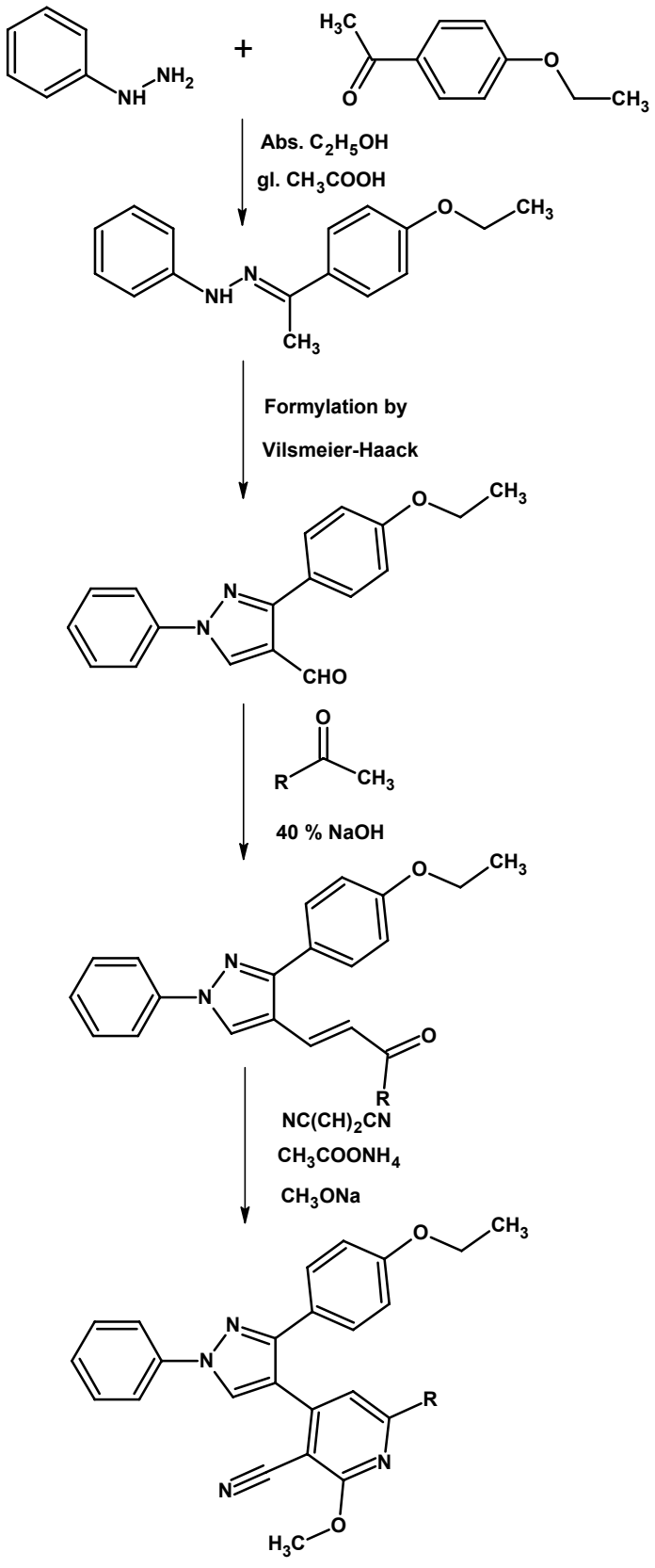


Type - (XI) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (XI) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-6-(*p*-BROMOPHENYL)-PYRIDINES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

See [A] Part-I, Section-I (C).

(D) Synthesis of 2-Methoxy-3-cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-6-(*p*-bromophenyl)-pyridine

A mixture of 1-(*p*-bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one(4.87 g, 0.01 M), malononitrile (0.66 g, 0.01 M) and ammonium acetate (2.31 g, 0.03 M) in sodium methoxide(30 ml) and sodium methoxide (10 ml) (6.61g, 0.08M) dissolved in absoulte alcohol was refluxed for 8 hrs., poured into crushed ice. The solid obtained was filtered, washed with water and crystallised from DMF. Yield 62%, m.p.168^{o}C. ($C_{30}H_{23}BrN_4O_2$; required: C, 65.34; H, 4.20; N, 10.16%; found: C, 65.30; H, 4.14; N, 10.10%).

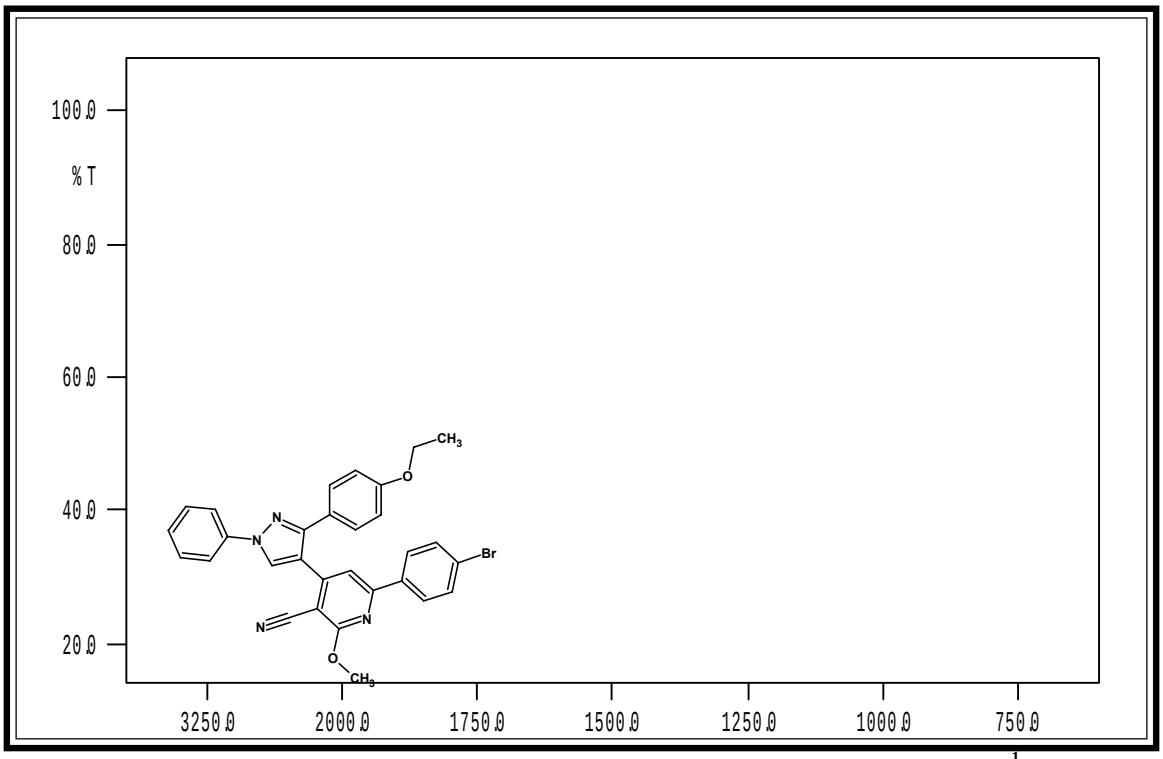
TLC Solvent System :Ethyl acetate : Hexane (2 : 8)

Similarly other 2-methoxy-3-cyano-4-(1',N-phenyl-3'-p-ethoxyphenyl-pyrazol-4'-yl)-6-(*p*-bromophenyl)-pyridine were synthesized. The physical data are recorded in Table No.11.

[D] Antimicrobial activity of 2-Methoxy-3-cyano-4-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-6-aryl-pyridine

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.11.

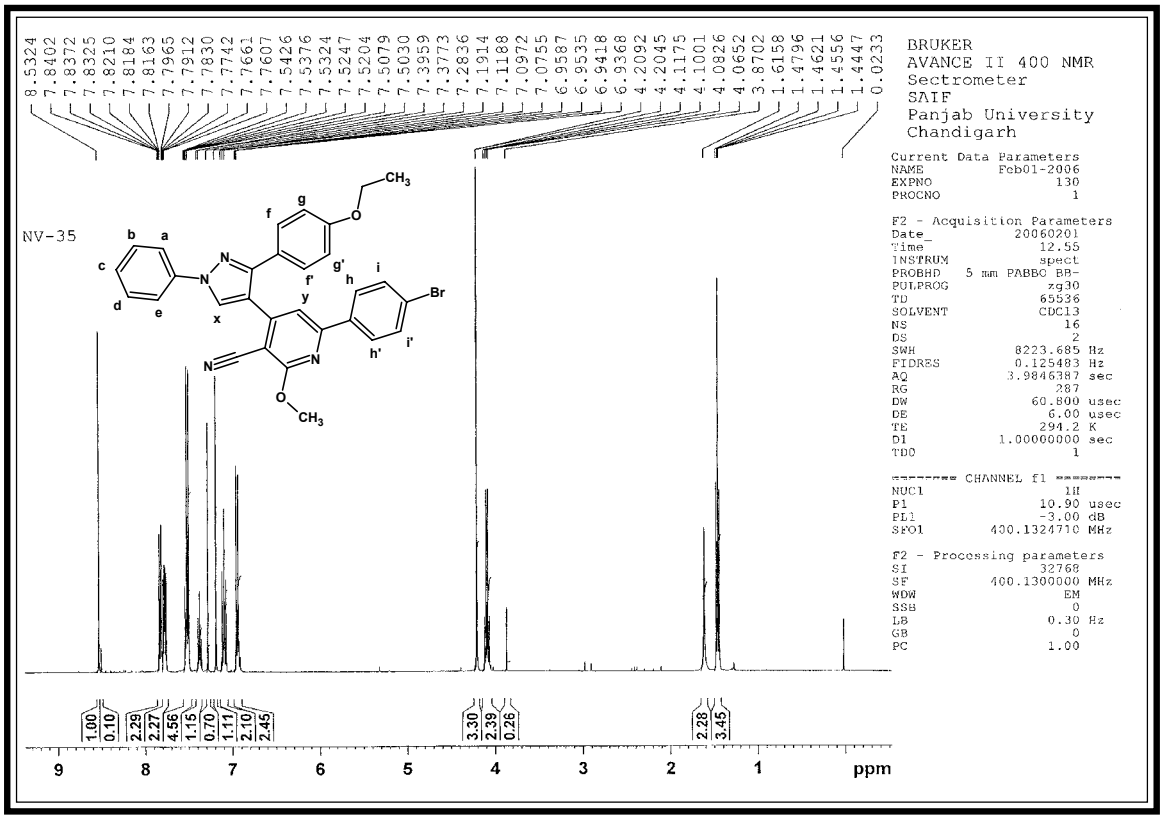
IR SPECTRAL STUDY OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-(*p*-BROMOPHENYL) PYRIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2943	2975-2950	413
$-CH_3$	C-H str. (sym.)	2846	2880-2860	
	C-H i.p.def. (asym.)	1461	1470-1435	
	C-H o.o.p. def. (sym.)	1344	1390-1370	
Aromatic	C=H str.	3076	3080-3010	414
	C=C str.	1500	1585-1480	
	C-H i.p. def.	1095	1125-1000	
	C-H o.o.p. def	825	835-810	
Pyrazole	C=N str.	1587	1630-1590	415
moiety	C-N str.	1157	1230-1020	
	C-Br str.	758	600-800	413
Ether	C-O-C str. (asym.)	1242	1275-1200	413
	C-O-C str. (sym.)	1037	1075-1020	
Pyridine ring	C^{O}N str.	2219	2240-2120	420
	C=N str..	1558	1650-1580	
	C=C str.	1500 (overlapped)		

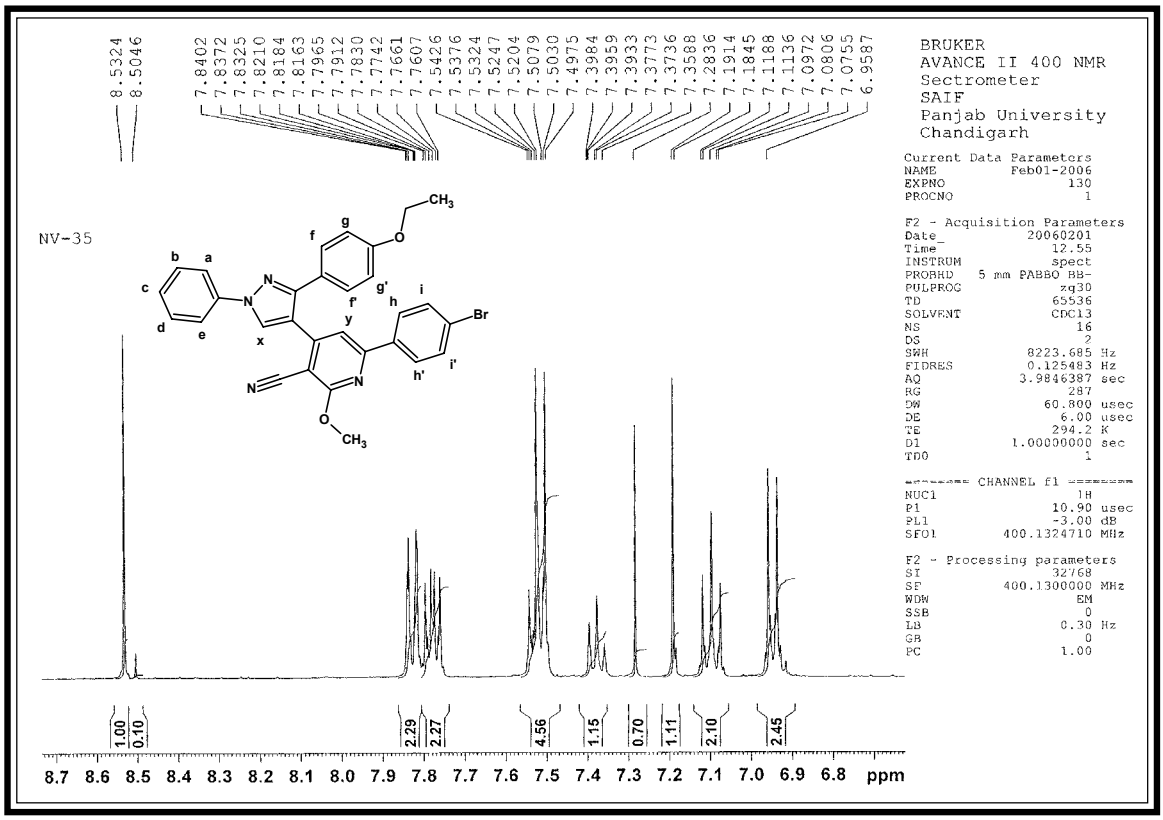
PMR SPECTRAL STUDY OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-(*p*-FLUOROPHENYL) PYRIDINE



Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.45-1.61	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.9
2.	4.08-4.20	2H	quartret	$-O\underline{CH}_2CH_3$	J_{CH_2}=7.0
3.	4.20	3H	singlet	$-OCH_3$	-
4.	6.93-6.95	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.7
5.	7.08-7.11	2H	triplet	Ar-H_{bd}	-
6.	7.35	1H	singlet	Ar-H_y	
7.	7.35-7.39	1H	triplet	Ar-H_c	-
8.	7.50-7.52	4H	multiplet	Ar-$H_{jj'}$Ar-$H_{ff'}$	J_{fg}=8.7
9.	7.76-7.78	2H	multiplet	Ar-$H_{a,e}$	
10.	7.82-7.84	2H	doublet	Ar-$H_{kk'}$	J_{kj}=8.2
11.	8.52	1H	singlet	CH_x	

EXPANDED AROMATIC REGION



IR SPECTRAL STUDY OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

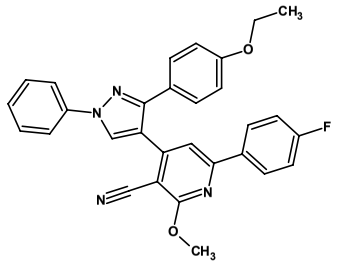
Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Sr. No.	R	$C^{o}N$ str.
11a	C_6H_5-	2215
11b	4-OCH_3-C_6H_4-	2210
11c	4-CH_3-C_6H_4-	2219
11d	4-Cl-C_6H_4-	2220
11e	4-F-C_6H_4-	2212
11f	4-Br-C_6H_4-	2214
11g	4-OH-C_6H_4-	2219
11h	2-OH-C_6H_4-	2220
11i	4-NO_2-C_6H_3-	2222
11j	2-NO_2-C_6H_3-	2212
11k	2-C_4H_3-	2218
11l	4-NH_2-C_6H_4-	2210

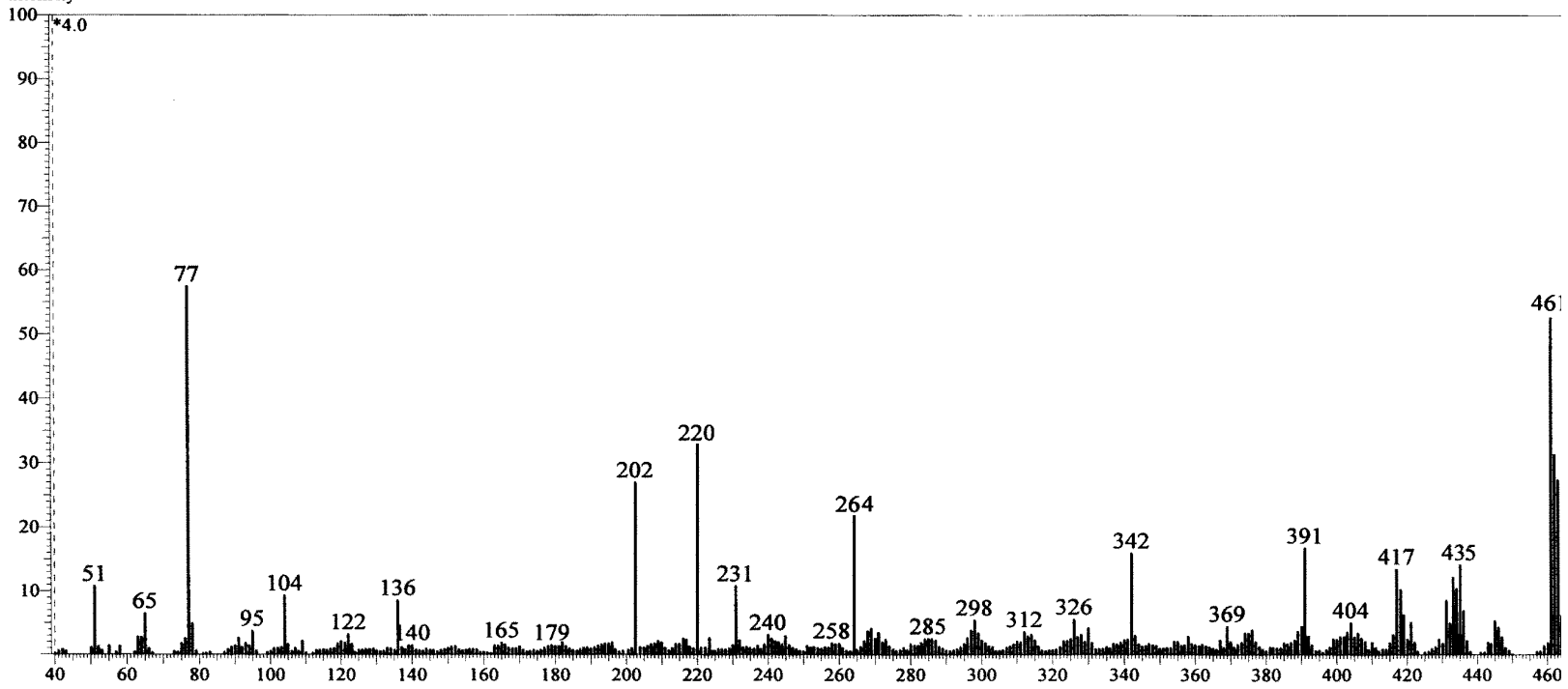
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 2/17/2006 3:44:42 PM
Sample Name	: NV-23
Sample ID	: NV-23
Data File	: C:\GCMSsolution\Data\H.H.PAREKH\NV-23.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt



Line#:1 R.Time:7.8(Scan#:895)
MassPeaks:411 BasePeak:490(1611418)
RawMode:Averaged 7.2-8.0(834-930)
BG Mode:Averaged 14.3-16.9(1678-1998)
intensity



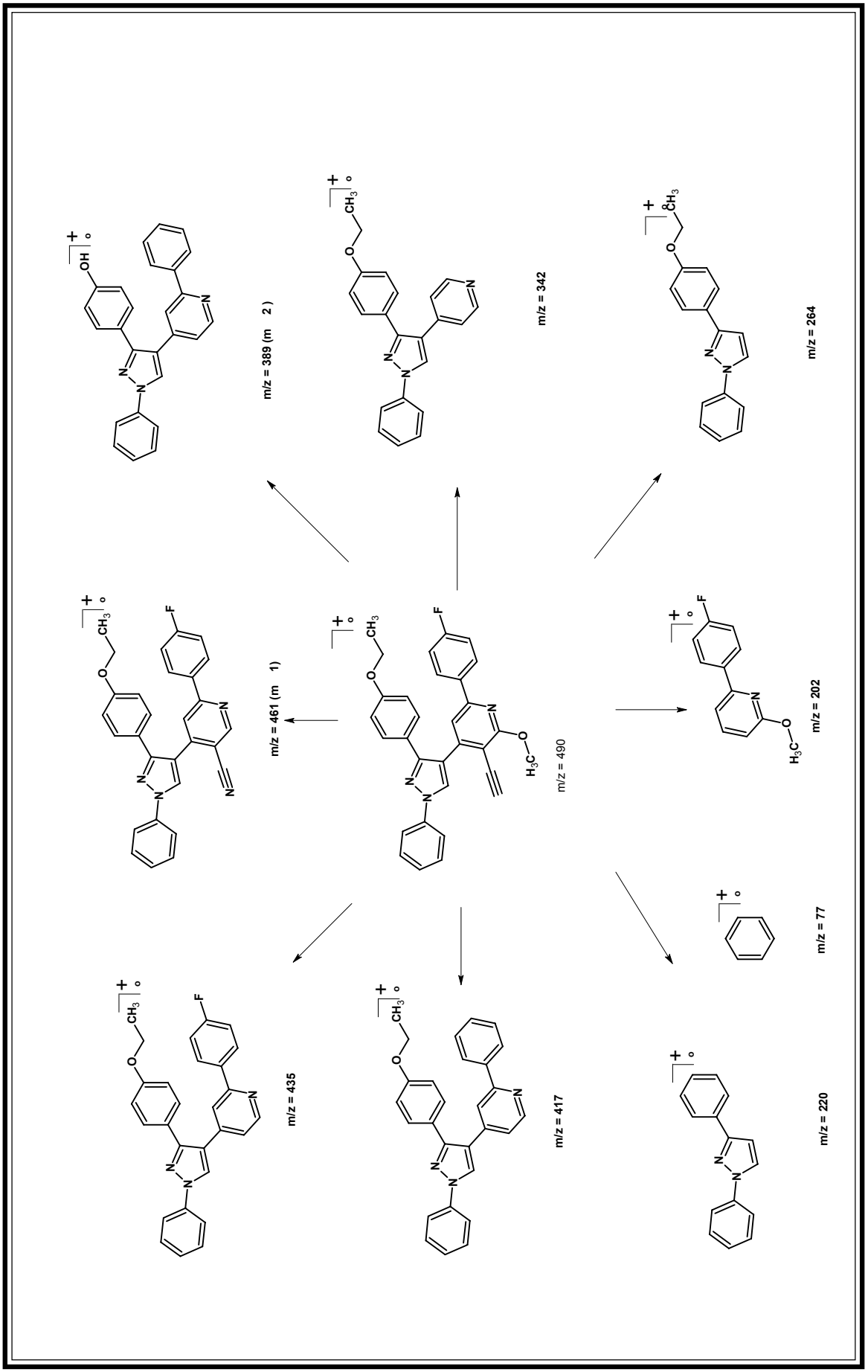
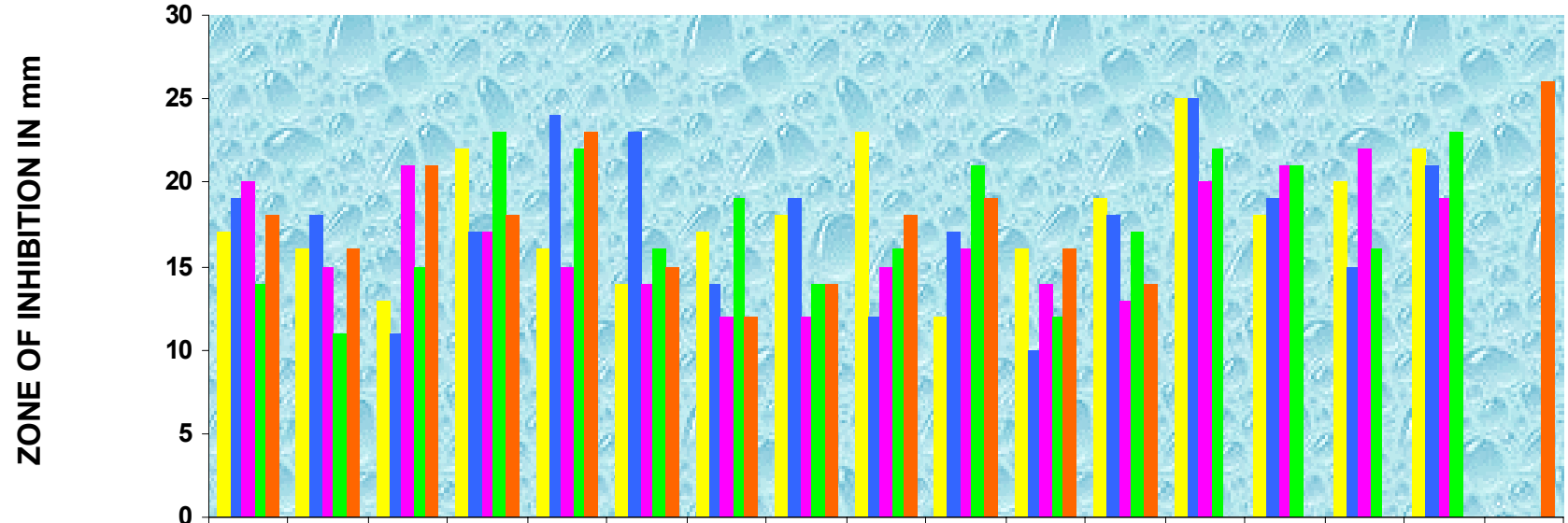

m/z = 490
m/z = 461 (m 1)
m/z = 435
m/z = 417
m/z = 389 (m 2)
m/z = 342
m/z = 264
m/z = 220
m/z = 202
m/z = 77

TABLE-11 : PHYSICAL CONSTANTS OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-ARYL PYRIDINES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
11a	C_6H_5-	$C_{30}H_{24}N_4O_2$	472	154	0.50	65	11.86	11.80
11b	4-OCH_3-C_6H_4-	$C_{31}H_{26}N_4O_3$	502	196	0.54	59	11.15	10.10
11c	4-CH_3-C_6H_4-	$C_{31}H_{26}N_4O_2$	486	244	0.62	70	11.51	10.46
11d	4-Cl-C_6H_4-	$C_{30}H_{23}ClN_4O_2$	506	186	0.69	63	11.05	10.45
11e	4-F-C_6H_4-	$C_{30}H_{23}FN_4O_2$	490	201	0.53	60	11.42	11.38
11f	4-Br-C_6H_4-	$C_{30}H_{23}BrN_4O_2$	551	168	0.54	62	10.16	10.10
11g	4-OH-C_6H_4-	$C_{30}H_{24}N_4O_3$	488	199	0.57	69	11.47	11.42
11h	2-OH-C_6H_4-	$C_{30}H_{24}N_4O_3$	488	180	0.66	70	11.47	11.41
11i	4-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_4$	517	147	0.51	59	13.53	13.47
11j	3-NO_2-C_6H_4-	$C_{30}H_{23}N_5O_4$	517	150	0.56	60	13.53	13.48
11k	2-C_4H_3-	$C_{28}H_{22}N_4O_2S$	476	178	0.55	63	11.71	11.66
11l	4-NH_2-C_6H_4-	$C_{30}H_{25}N_5O_2$	487	183	0.49	64	14.36	14.30

*TLC Solvent System :Ethyl acetate : Hexane (2 : 8)

GRAPHICAL CHART NO. 11 : ANTIMICROBIAL ACTIVITY OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-ARYL PYRIDINES



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	17	16	13	22	16	14	17	18	23	12	16	19	25	18	20	22	0
S. aureus	19	18	11	17	24	23	14	19	12	17	10	18	25	19	15	21	0
E. aerogenes	20	15	21	17	15	14	12	12	15	16	14	13	20	21	22	19	0
P. aeruginosa	14	11	15	23	22	16	19	14	16	21	12	17	22	21	16	23	0
A. niger	18	16	21	18	23	15	12	14	18	19	16	14	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

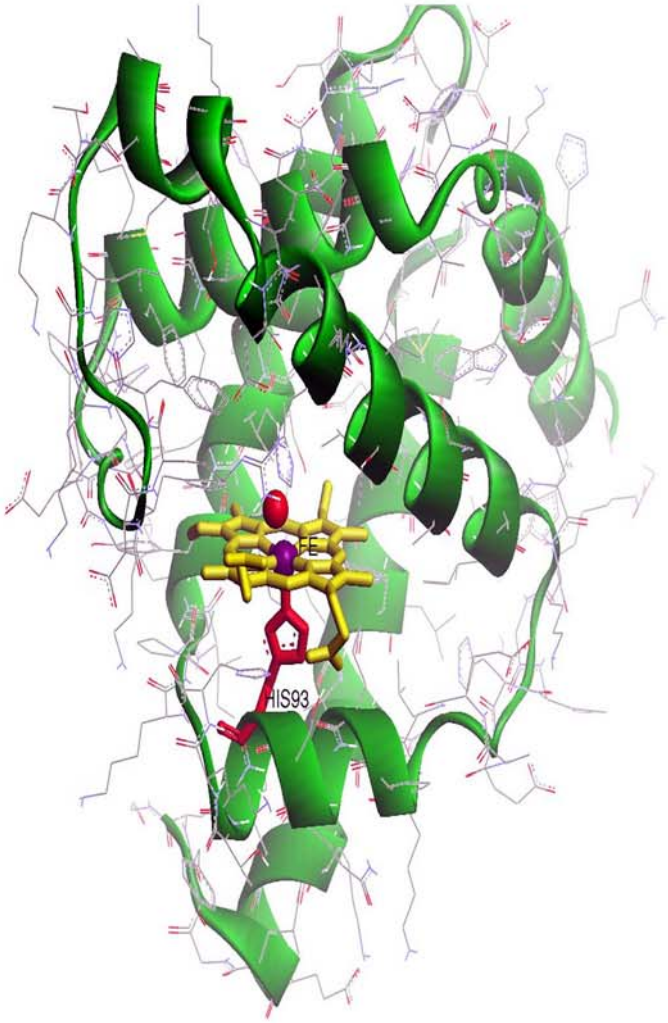
From the experimental data it has been concluded that all the compounds were mildly active against Gram positive bacterial strains except R=4-chlorophenyl and 4-nitrophenyl which showed highest activity against ***B.coccus*** and R=4-bromophenyl and 4-fluorophenyly which showed highest activity against ***S.aureus***.

In case of Gram negative bacterial strains, the compound bearing R= 4-tolyl have exhibited significant activity against ***E.aerogenes.*** The compounds bearing R=3-nitrophenyl,4-chlorophenyl and 4-fluorophenyl have shown maximum activity against ***P.aeruginosa***.

ANTIFUNGAL ACTIVITY

All the compounds were mildly active against ***A.niger.*** Maximum activity was shown by the compounds bearing R=4-tolyl and 4-fluorophenyl.

The antibacterial activity was compared with standard drug viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

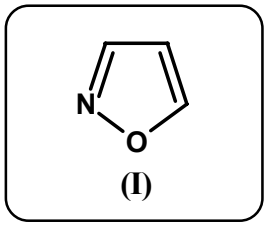


PART-VII

STUDIES ON ISOXAZOLES

INTRODUCTION

Isoxazole is a five membered heterocyclic compound having two hetero atom: oxygen at position 1 and nitrogen at position 2. It was shown to possess typical properties of an aromatic system under certain reaction conditions. Particularly in reducing or basic media, it becomes highly labile, yet it is easily cleaved when necessary.Thus, isoxazoles are very useful intermediates since the ring system stability allows the manipulation of substituents to give functionally complex derivatives. Consequently, isoxazole have become an important synthetic tool..



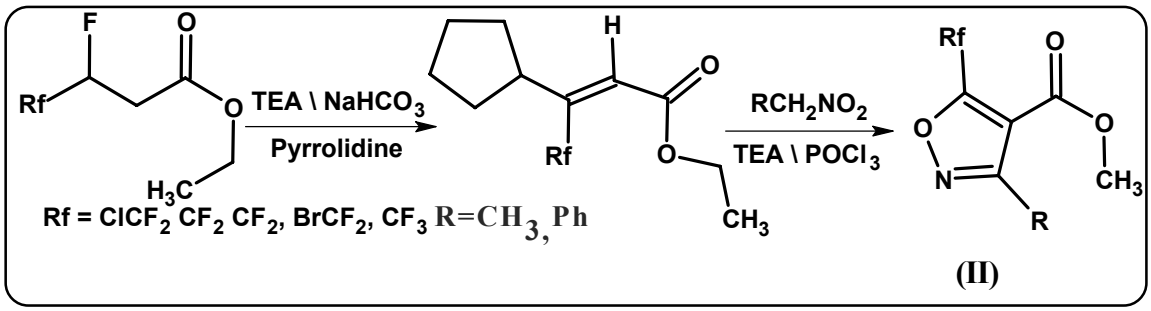
(I)

Claisen[321] first reported an isoxazole (I) for a product from the reaction of 1,3 diketone with hydroxylamine. The next important contribution to the chemistry of isoxazoles was made by Quelico[322] in 1945, when he began to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds.

SYNTHETIC ASPECTS

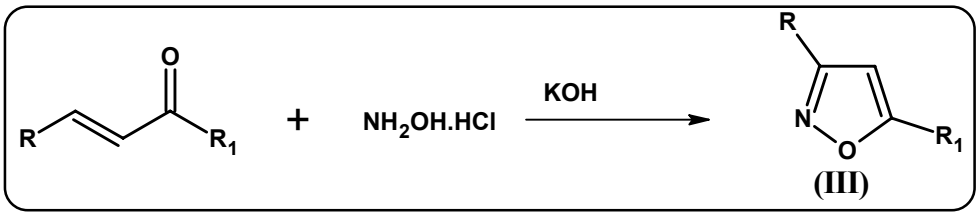
Isoxazoles can be prepared by various methods, which are described as under.

1. Tayade V. B. et al.[323] synthesized some new 3,5-diarylisoxazoles from the reaction of 2-aryl acetophenones with hydroxyl amine hydrochloride in presence of alkali.
2. By the reaction of nitrile oxide, TEA and $POCl_3$ with ethyl-3-perfluoroalkyl-3-pyrolidine-acrylates[324].

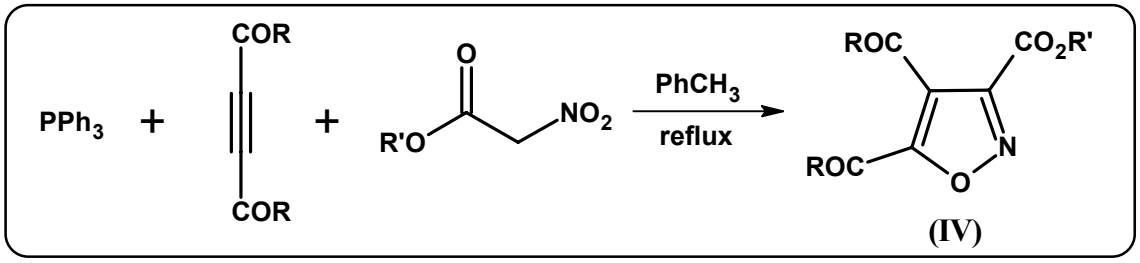


(II)

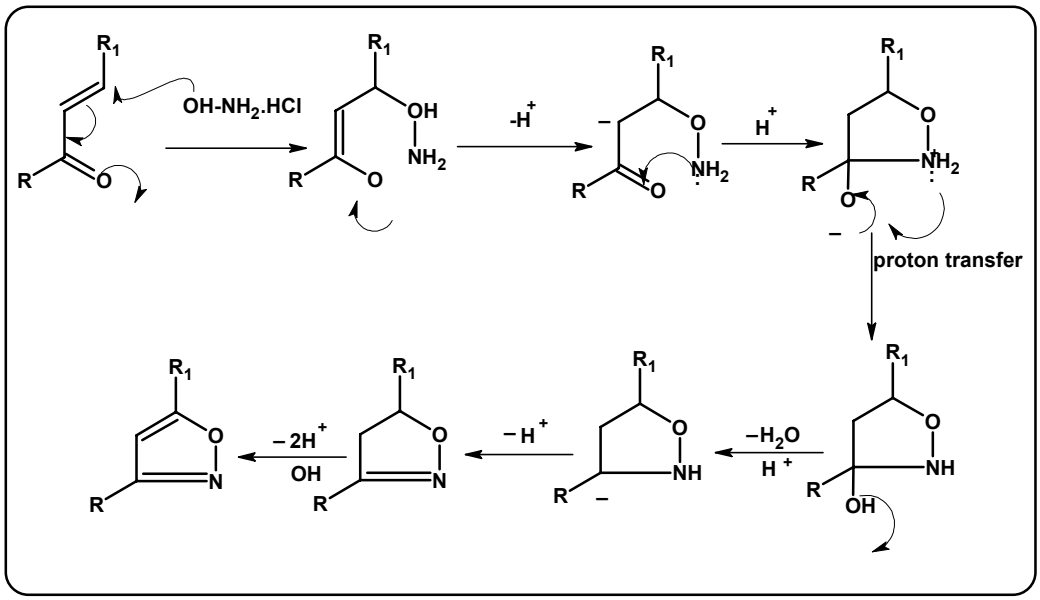
3. Crawley and Fan Shawe[325] prepared isoxazole from a,b-unsaturated carbonyl compounds, hydroxyl amine hydrochloride and KOH in methanol.



4. Issa and Loghman[326] have synthesised isoxazoles (IV) from activated acetylenes and alkyl 2-nitroethanoates in the presence of triphenylphosphine.

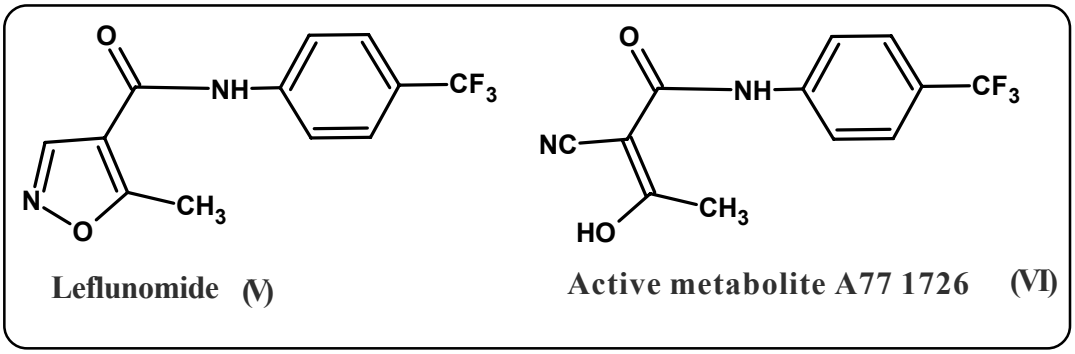


MECHANISM



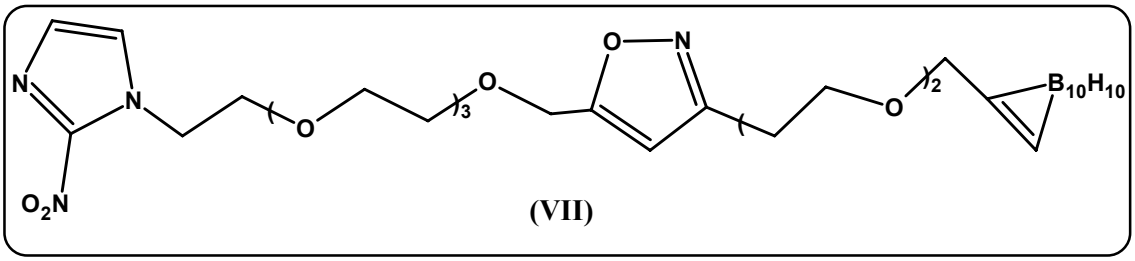
THERAPEUTIC IMPORTANCE

A class of isoxazole derivatives has been disclosed as having immuno suppressant activity. These heterocycles are rapidly converted *in vivo* to ring opened metabolites, hydroxyalkylidene-cynoacetamides, which we believed to be the active therepeutic agents. Leflunomide(V) is the lead compound of this new group of isoxazole derivatives that have been developed at Hoechst.



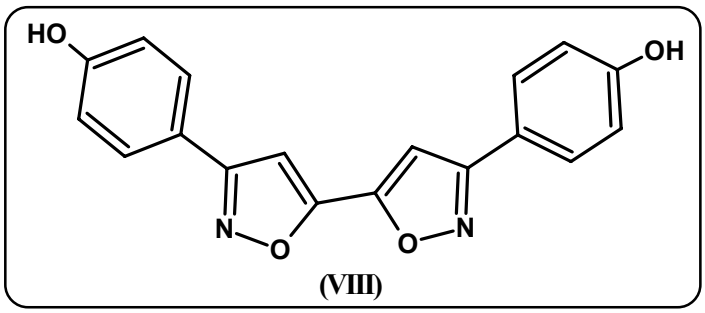
Leflunomide (V) **Active metabolite A77 1726 (VI)**

The psysiological effects of this classs of compounds, analogues of A77 1726(VI) and the parent isoxazoles were disclosed as useful for treatment of cancer[327]. These compounds exert an antiproliferactive effect through inhibition of receptor tyrosine kinases and have little effect on proliferation of normal cells since their inhibitory effect on DHOdehase is weak.TheDihydro isoxazoles can be used as linkers for joining chemically sensitive moieties.This is the case for isoxazole-linked nitroimidazole-carborane (VII) used for targeting hypoxic tumors[328].



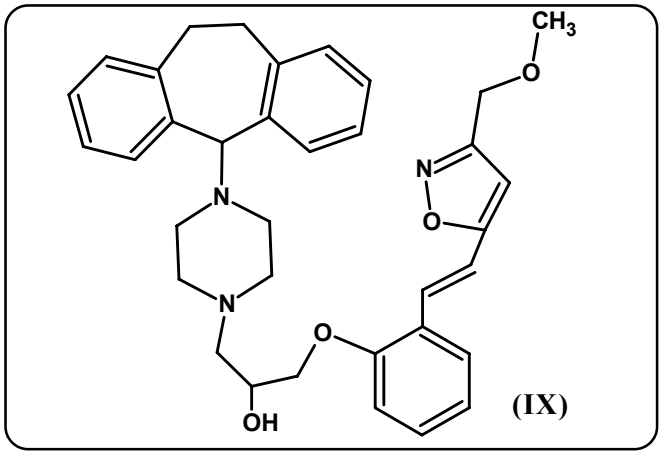
(VII)

Some isoxazole analogs of retinoids exhibited good antiproliferative activity and capability to induce differentiaon *in vitro* culture tumor cell lines[329].Compound (VIII) is a representative example of bis-isoxazole derivatives disclosed to have anticancer properties[330].



(VIII)

The compound (IX) is chosen among a wide series of 1-amino-3-phenoxy propane derivatives claimed as antineoplastic enhancers which are able to modulate the multi-drug resistance of tumor cells to various chemotherpeutic agents[331].



(IX)

Over and above the isoxazoles posses wide range of therapeutic activites like,

(a) Cardiovascular[332,333]

(b) Antiviral[334,335]

(c) CNS active[336,337]

(d) Analgesic[338]

(e) Anticonvulsant[339]

(f) Fungicidal[340]

(g) Anticholestermic[341]

(h) Hypoglycemic[342]

(i) Antileukemic[343]

(j) Antipyretic[344]

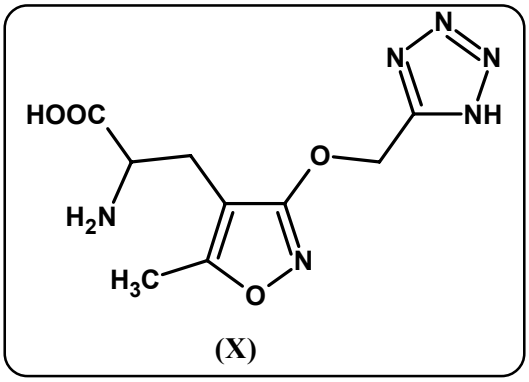
(k) Antiinflammatory[345]

(l) Nematocidal[346]

(m) Muscle relaxant[347]

(n) Antidiabetic[348]

R. Ulrich et. al.[349] have synthesised isoxazole derivatives and reported their adrenergic antagonist activity. Qi Chuanmin et. al.[350] have discovered isoxazoles as herbicidal. Wu Chengde et. al.[351] have synthesised isoxazole derivatives as endothelin activity modulators. Some of the compounds exhibited IC_{50} values of 0.0015 ± 0.0014 mM for ET_A receptors and 0.324 ± 0.78 mM for ET_B receptors. Caroline and co-workers[352] have studied isoxazoles which have been used for the clinical trials of asthama. Bente Frolund et. al.[353] have reported tetrazolylisoxazole amino acids as ionotropic glutamate receptor antagonists (X).

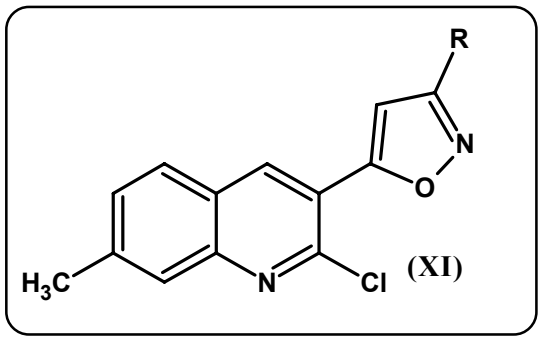


(X)

Barbachyn M. R. et al.[354] have described the phenylisoxazolines as novel and viable antibacterial agents active against Gram-positive pathogens. Salter M. W. et al.[355] have prepared some novel isoxazole as cellular neuroplasticity mechanisms mediating pain persistence.Mehlisch D. R. et al.[356] have synthesized isoxazole derivative as analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. Welsing P. M. et al.[357] have documented the isoxazoles as tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands.

CONTRIBUTION FROM OUR LABORATORY

H. H. Parekh et al.[358] have synthesised 3-(*p*-methoxyphenyl)-5-(2'-chloro-7'-methylquinolin-3'-yl)-isoxazole (XI) and studied their biological activity.

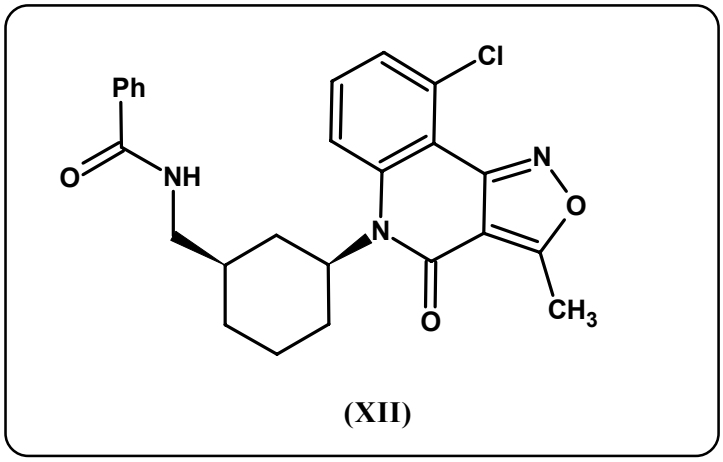


(XI)

V. B. Patel and co-workers[359] have prepared isoxazoles bearing sulphonamide moiety and reported their antimicrobial activity. Ketan Hirpara et. al.[360] have synthesised isoxazoles as antitubercular agents. A. V. Dobaria et. al.[361] have described the isoxazole derivatives and their use as antimicrobial agents. B. P. Kansagara et. al.[362] have demonstrated various isoxazoles and tested their antimicrobial activity.

Recently, H. S. Yathirajan et. al.[363] have synthesised novel 4-(5-methyl-3-phenylisoxazole-4-yl) benzene-sulfonamide ethylmethyl ketone used as non-sterodal antiinflammatory drug.Bente Frolund et. al.[364] have reported tetrazolyl isoxazole amino acids as ionotropic glutamate receptor antagonists. Bryan H. Norman et. al.[365] have reported cyclohexyl-linked tricyclic isoxazoles as potent and selective modulators of the multidrug resistance protein (MRP1)(XII).

Jie-Fei Cheng et. al.[366] have prepared isoxazole derivatives as MCD inhibitors. Wiles J. A. and co-workers[367] have prepared fluoroisothiazolo pyridone derivatives which exhibited antibacterial activity and inhibitory activities against DNA gyrase and topoisomerase IV.



(XII)

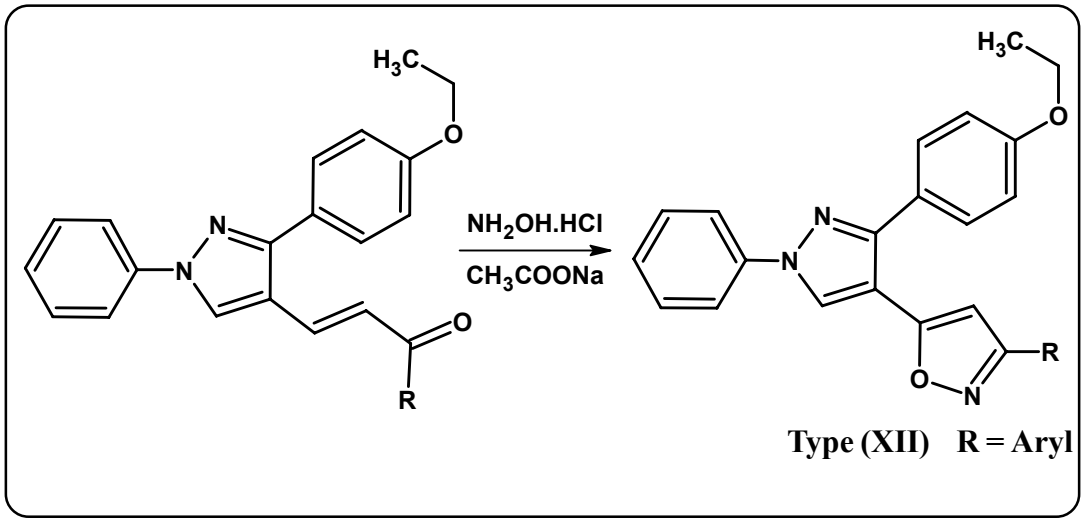
With a view to getting better therapeutic value, it was contemplated to synthesise isoxazole derivatives in corporating pyrazole as parent molecule, to enhance the overall activity of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLES

With a view to achieving better drug potency isoxazole derivatives of type (XII) have been prepared by the condesation of chalcones of type (I) with hydroxylamine hydrochloride in the presence of sodium acetate in glacial acetic acid. The chalcones were synthesised by the condensation of 1,N-phenyl-3-*P*-ethoxyphenyl-4-formyl pyrazole with various aromatic ketones.

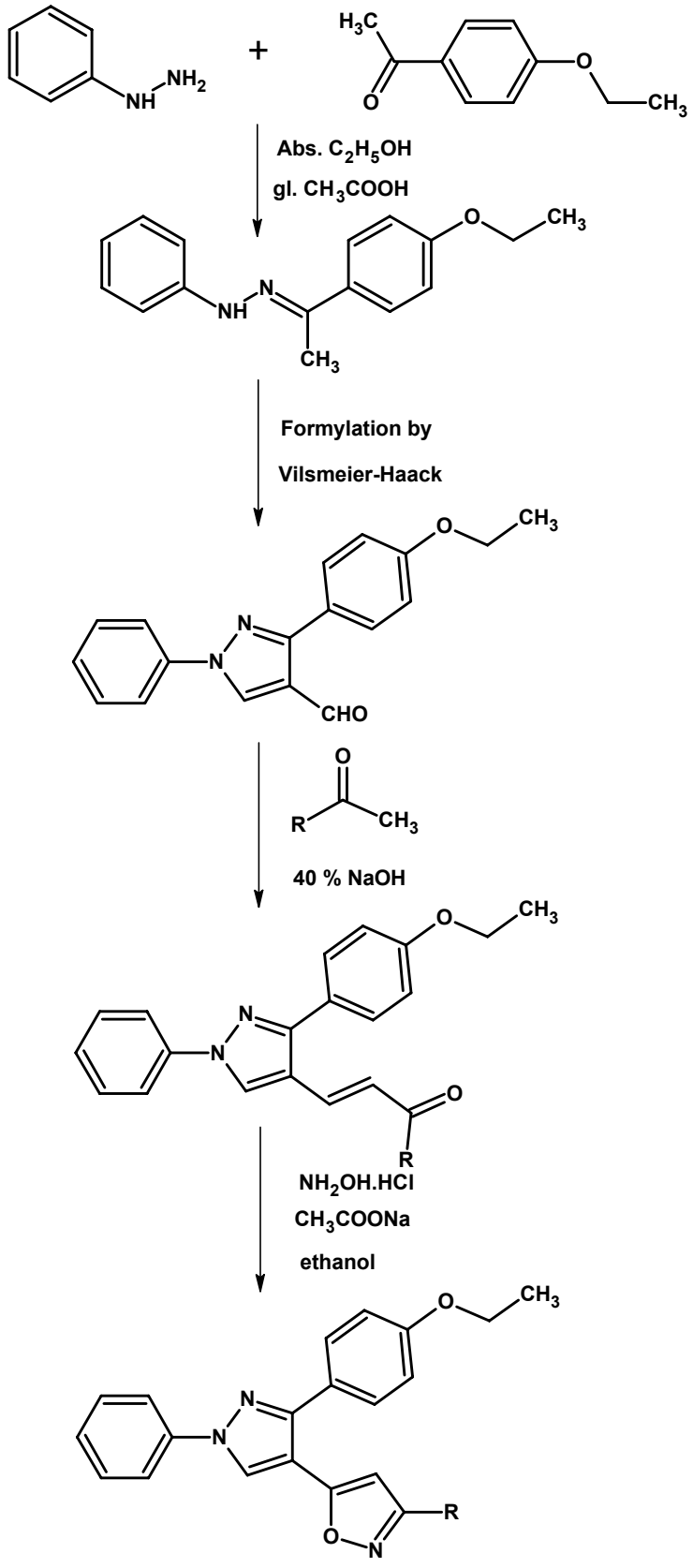


Type (XII) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (XII) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of 1-(*p*-Bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one

See [A] Part-I, Section-I (C).

(D) Synthesis of 3-(*p*-Bromophenyl)-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-isoxazole

A solution of anhydrous sodium acetate (1.46g, 0.02 M) in a minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (1.4 g, 0.02 M) in ethanol (20 ml). This solution was added to a solution of 1-(*p*-bromophenyl)-3-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-2-propen-1-one (4.73 g, 0.01 M) in ethanol (25 ml). The mixture was heated under reflux on waterbath for 12 hrs. The product was isolated and recrystallised from ethanol. Yield 68%, m.p. 145^{o}C ($C_{26}H_{20}BrN_3O_2$; Required : C, 64.21; H, 4.14; N, 8.64; Found : C, 64.15; H, 4.09; N, 8.58%).

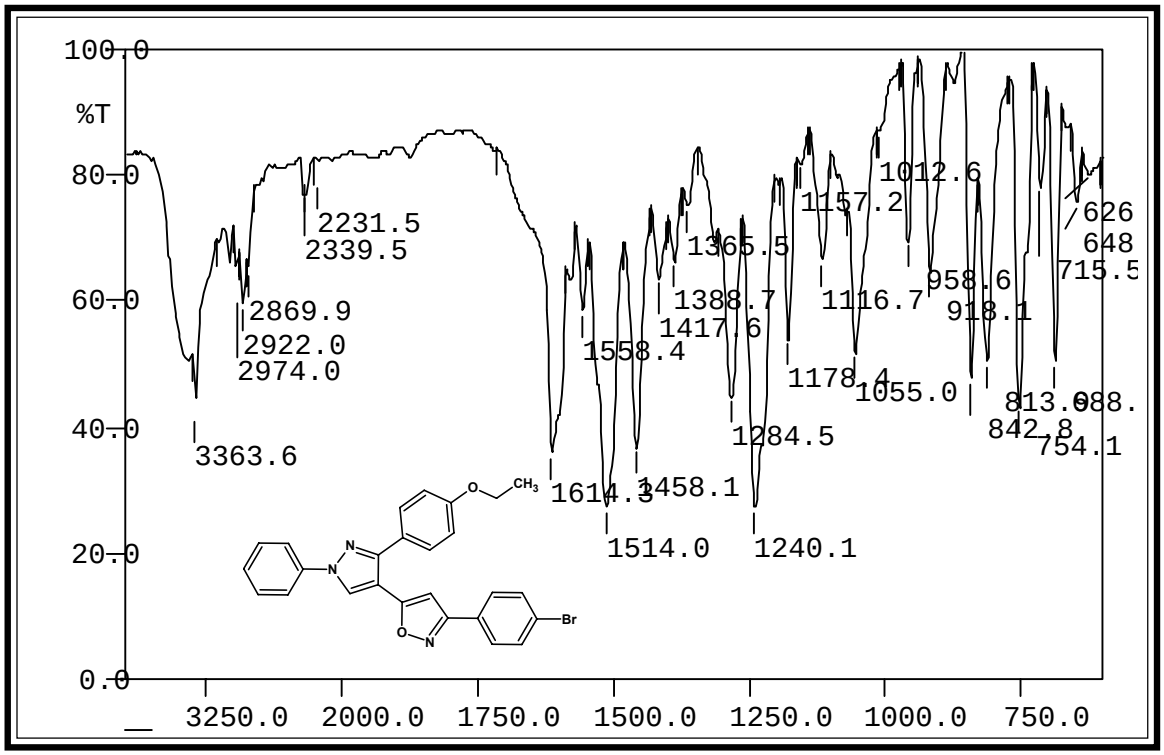
TLC solvent system : Acetone : Benzene (1.5 : 8.5).

Similarly other substituted isoxazoles have been prepared. The physical data are recorded in Table No. 12.

(E) Antimicrobial activity of 3-Aryl-5-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-isoxazoles

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 12.

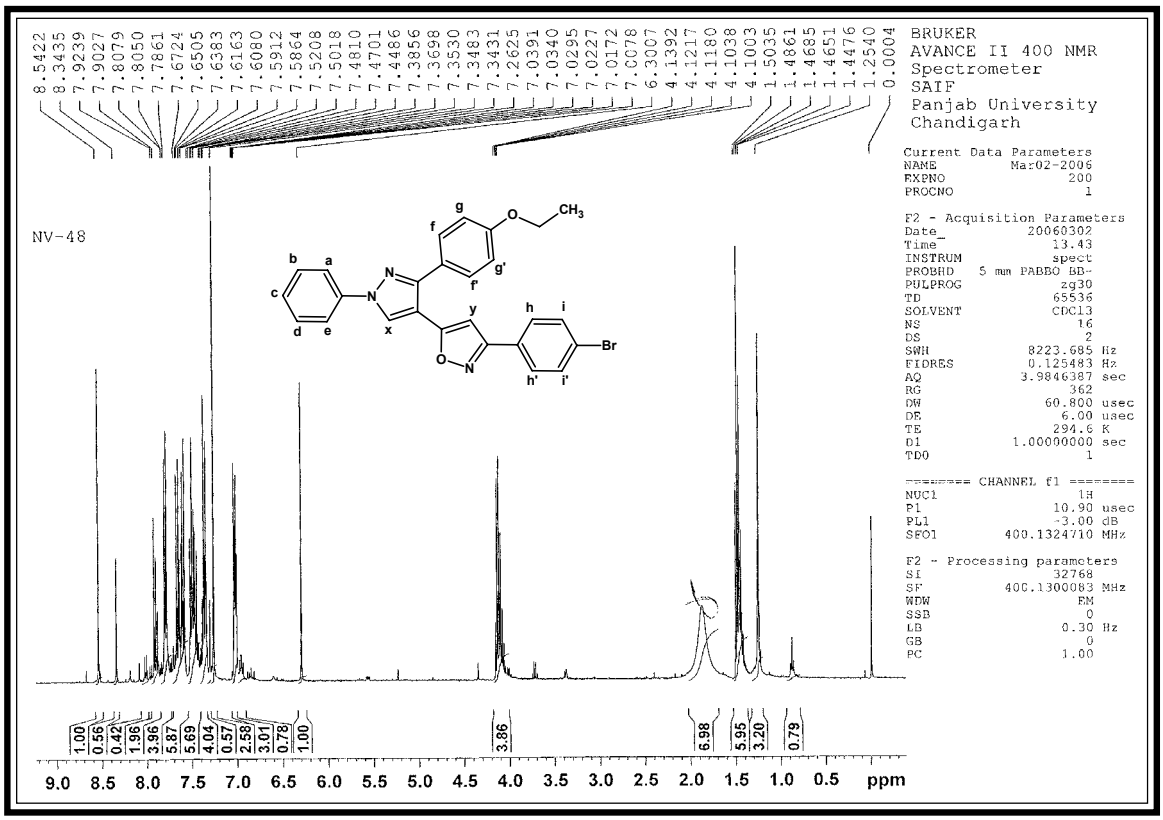
IR SPECTRAL STUDY OF 3-(*p*-BROMOPHENYL)-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2974	2975-2950	413
$-CH_3$	C-H str. (sym.)	2869	2880-2860	
	C-H i.p.def. (asym.)	1458	1470-1435	
	C-H o.o.p. def. (sym.)	1388	1390-1370	
Aromatic	C=C str.	1514	1585-1480	414
	C-H i.p. def.	1116	1125-1090	
	C-H o.o.p. def	842	835-810	
Pyrazole	C=N str.	1614	1630-1590	415
moiety	C-N str.	1178	1230-1020	
	C-Br str.	754	600-800	413
Ether	C-O-C str. (asym.)	1240	1275-1200	413
	C-O-C str. (sym.)	1055	1075-1020	
Isoxazole	C=C str.	1514 (overlapped)	1580-1530	413
	C=N str.	1614	1470-1460	
	N-O str.	813	850-800	

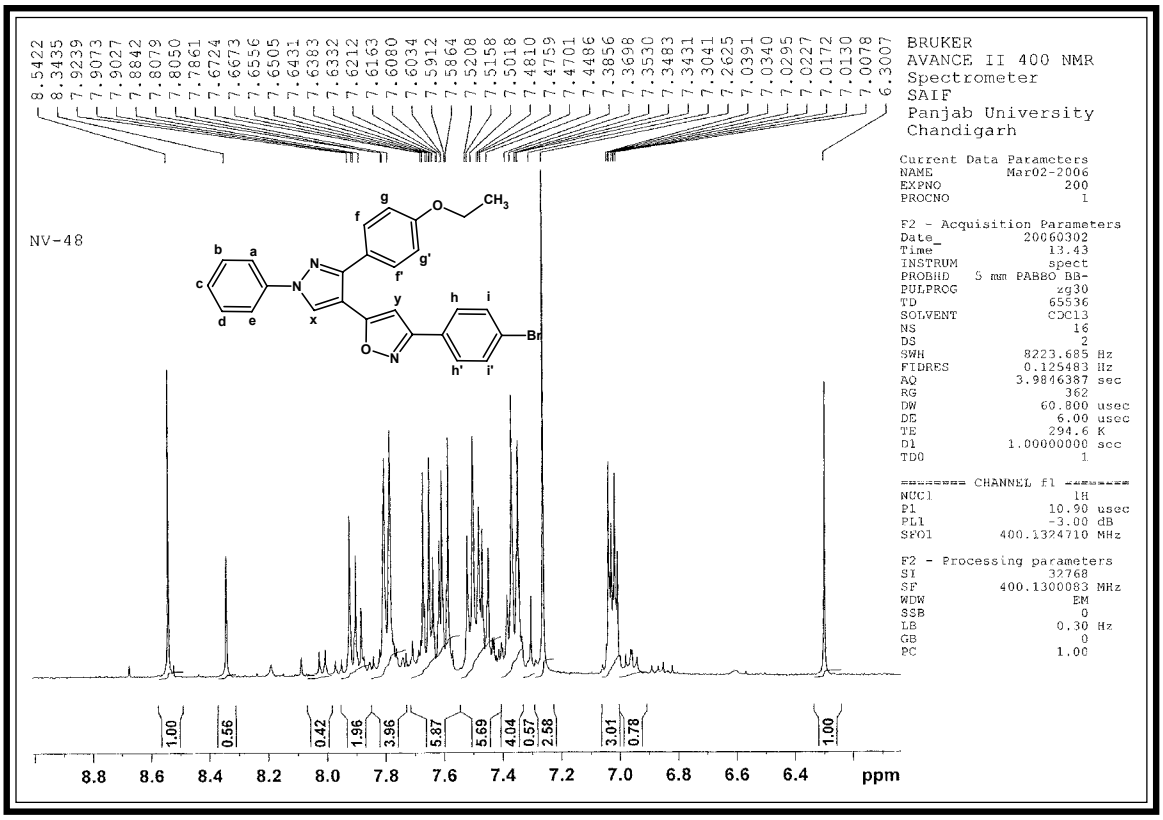
PMR SPECTRAL STUDY OF 3-(*p*-BROMOPHENYL)-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLE

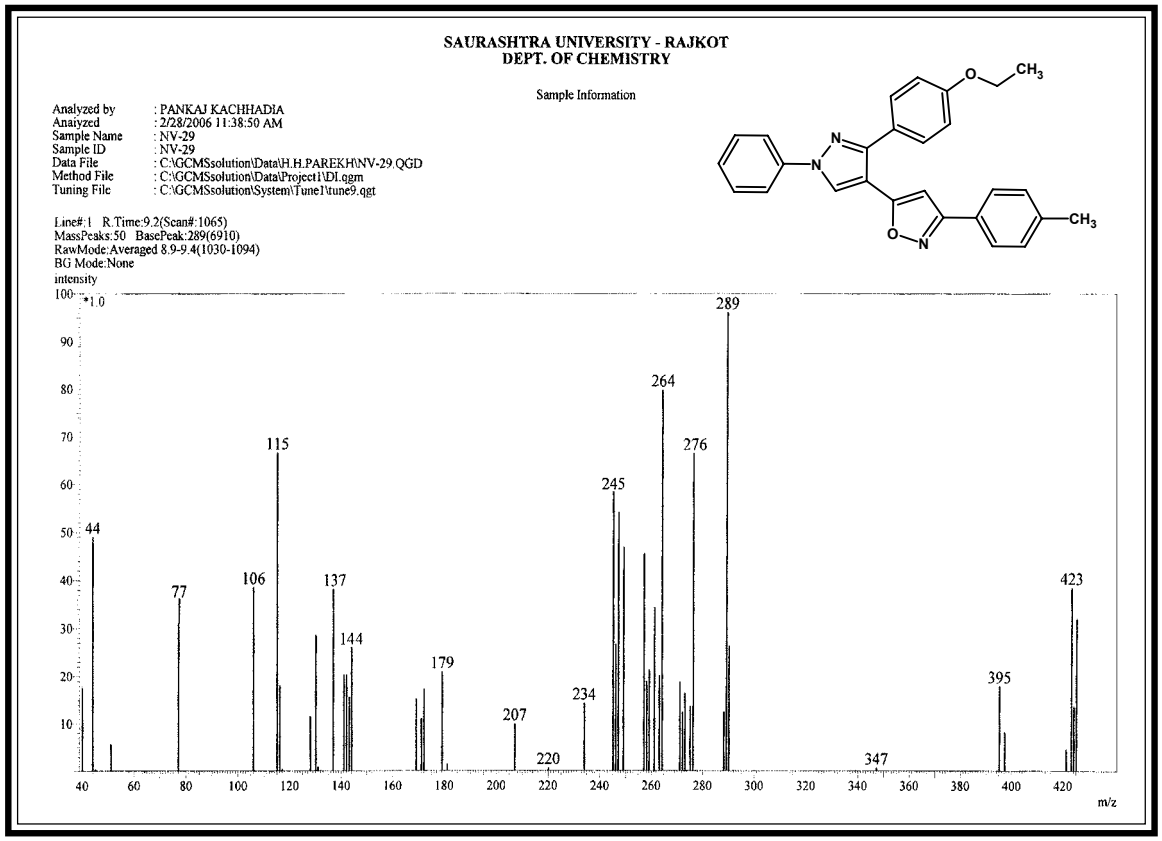


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.46-1.50	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.9
2.	4.10-4.13	2H	quartet	$-O\underline{CH}_2CH_3$	J_{CH_3}=6.8
3.	6.30	1H	singlet	Ar-H_y	-
4.	7.01-7.03	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.4
5.	7.34-7.36	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.3
6.	7.47-7.52	3H	multiplet	Ar-H_{abd}	-
7.	7.60-7.67	3H	multiplet	Ar-H_e,Ar-$H_{hh'}$	-
8.	7.78-7.80	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.4
9.	7.90-7.92	1H	triplet	Ar-H_c	-
10.	8.54	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION





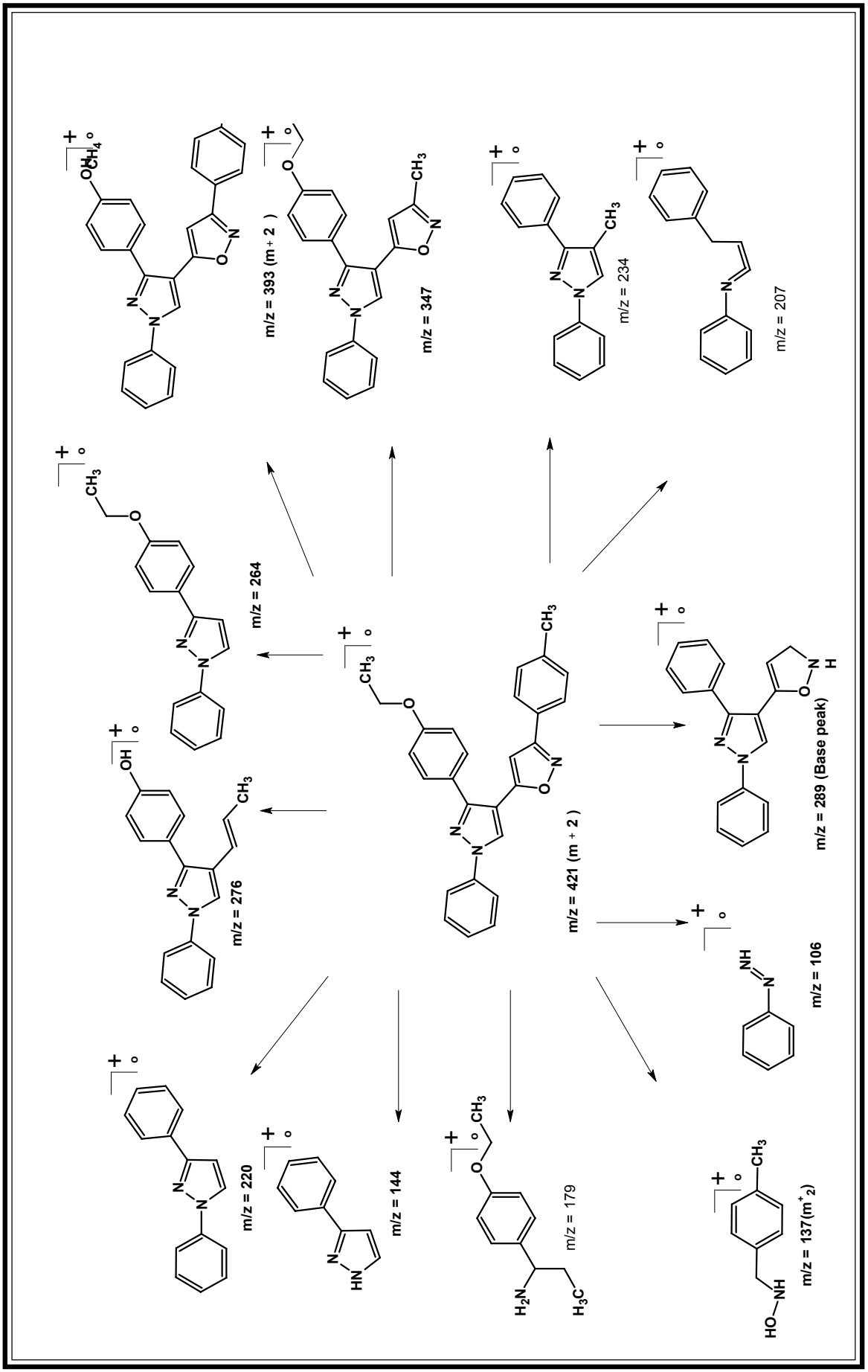
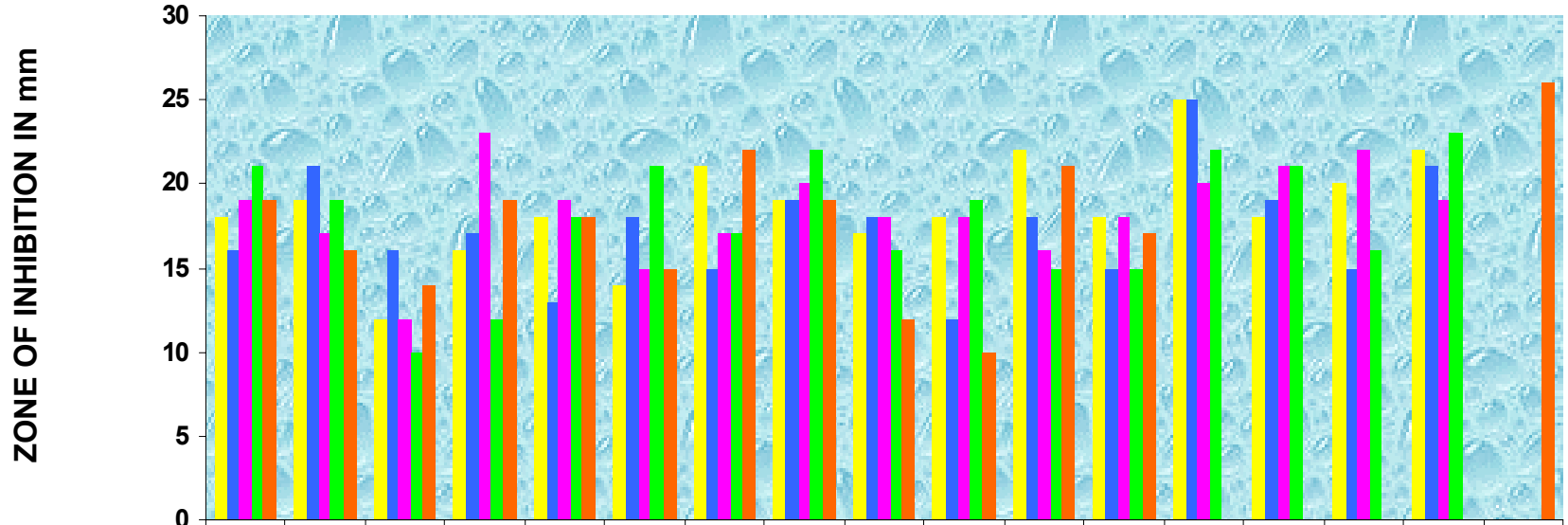

m/z = 421 (m + 2)
m/z = 393 (m+ 2)
m/z = 347
m/z = 289 (Base peak)
m/z = 264
m/z = 276
m/z = 234
m/z = 207
m/z = 220
m/z = 144
m/z = 179
m/z = 137(m+2)
m/z = 106

TABLE-12 : PHYSICAL CONSTANTS OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
12a	C_6H_5-	$C_{26}H_{21}N_3O_2$	407	143	0.52	68	10.31	10.26
12b	4-NH_2-C_6H_4-	$C_{26}H_{22}N_4O_2$	422	198	0.63	73	13.26	13.21
12c	4-Cl-C_6H_4-	$C_{26}H_{20}ClN_3O_2$	441.5	167	0.53	68	9.51	9.46
12d	4-Br-C_6H_4-	$C_{26}H_{20}BrN_3O_2$	486	145	0.51	68	8.64	8.58
12e	4-F-C_6H_4-	$C_{26}H_{20}FN_3O_2$	425	155	0.40	71	9.88	9.83
12f	2-OH-C_6H_4-	$C_{26}H_{21}N_3O_3$	423	214	0.54	68	9.92	9.87
12g	4-OH-C_6H_4-	$C_{26}H_{21}N_3O_3$	423	233	0.64	65	9.92	9.85
12h	4-OCH_3-C_6H_4-	$C_{27}H_{23}N_3O_3$	437	175	0.51	83	9.60	9.55
12i	4-CH_3-C_6H_4-	$C_{27}H_{23}N_3O_2$	421	158	0.59	59	9.97	9.94
12j	3-NO_2-C_6H_4-	$C_{26}H_{20}N_4O_4$	452	169	0.61	60	12.38	12.34
12k	4-NO_2-C_6H_4-	$C_{26}H_{20}N_4O_4$	452	118	0.54	78	12.38	12.32
12l	2-C_4H_3S-	$C_{24}H_{19}N_3O_2S$	413	201	0.61	59	10.16	10.12

*TLC Solvent System : Acetone : Benzene (1.5-8.5)

GRAPHICAL CHART NO. 12 : ANTIMICROBIAL ACTIVITY OF 3-ARYL-5-(1',N-PHENYL-3'-*p*-ETHOXY-ETHOXYPHENYL-PYRAZOL-4'-YL)-ISOXAZOLES



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Griseofulvin
B. coccus	18	19	12	16	18	14	21	19	17	18	22	18	25	18	20	22	0
S. aureus	16	21	16	17	13	18	15	19	18	12	18	15	25	19	15	21	0
E. aerogenes	19	17	12	23	19	15	17	20	18	18	16	18	20	21	22	19	0
P. aeruginosa	21	19	10	12	18	21	17	22	16	19	15	15	22	21	16	23	0
A. niger	19	16	14	19	18	15	22	19	12	10	21	17	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been concluded from the experimental data that all the isoxazole derivatives (XII) markedly inhibit the growth of Gram positive bacteria and Gram negative bacteria.

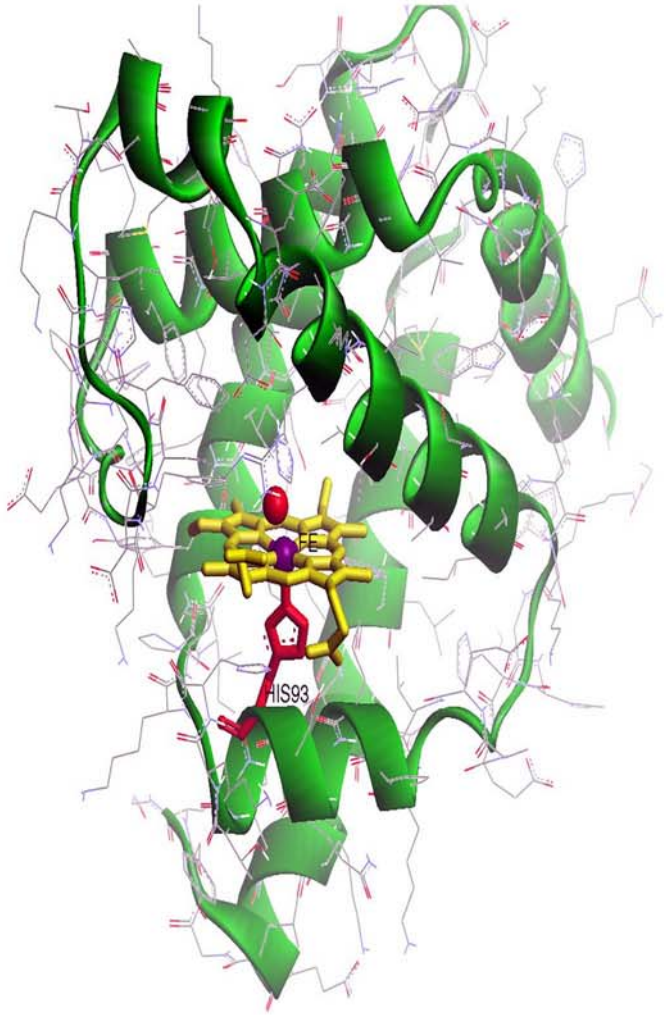
All compounds showed moderate activity against Gram positive bacteria. However, maximum activity was observed in compounds bearing R=4-hydroxyphenyl and 4-nitrophenyl against ***B.coccus*** whereas R=4-aminophenyl against ***S.aureus.***

In case of Gram negative bacterial strains, the maximum activity was displayed by the compounds bearing R=4-bromophenyl against ***E.aerogenes.*** While the compounds with R=phenyl, 4-methoxyphenyl, 2-hydroxyphenyl and 4-methoxyphenyl have shown considerable activity against ***P.aeruginosa.***

ANTIFUNGAL ACTIVITY

All compounds exhibited mild activity against ***A.niger*** except compound bearing R=4-hydroxyphenyl and 4-nitrophenyl which showed good activity against ***A.niger***.

The antibacterial activity was compared with standard drug viz.amoxicillin,benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity wascompared with standard drug viz. greseofulvin.



PART-VIII

STUDIES ON

α-ARYLAMINONITRILES

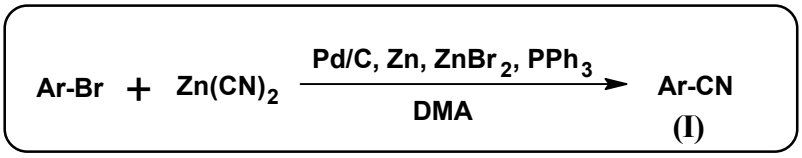
INTRODUCTION

*N*itriles are reported to possess various therapeutic activities, but due to their high toxicity, they have low therapeutic importance. The term 'Nitrile' was first introduced by Febung[368] in 1844. The first synthesis of nitrile has been reported by Wohler and Liebig[369] in 1832 and Poleuze[370] in 1834. They are very much useful as intermediates for various products such as acrylonitrile for plastic, synthetic rubber, fibers & phthalonitrile for dye stuff.

SYNTHETIC ASPECTS

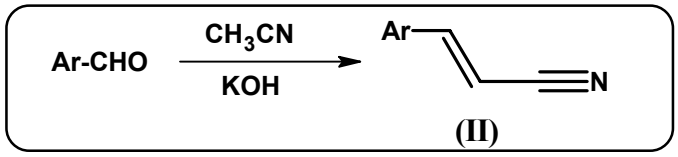
Few recent methods for the preparation of nitriles are as mentioned below.

1. From alkyl halides using KCN, tetraalkylammonium salt[371] and water in trace.
2. Masanori and Masahiko[372] have synthesised nitriles through cyanation of aryl/ heteroaryl bromides employing heterogeneous Pd/C.



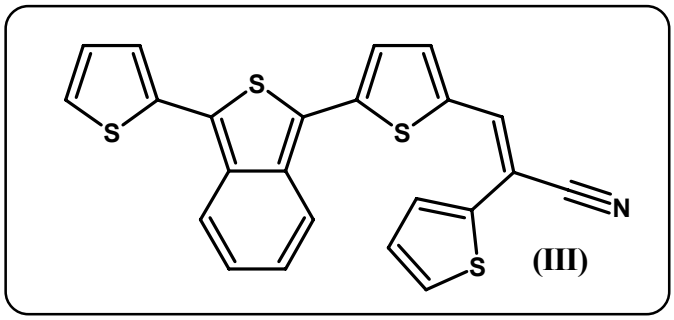
(I)

3. Stephen A et.al.[373] have synthesised E-& Z-cinnamonitrile from aryl aldehyde or ketones in the presence of acetonitrile and potassium hydroxide.



(II)

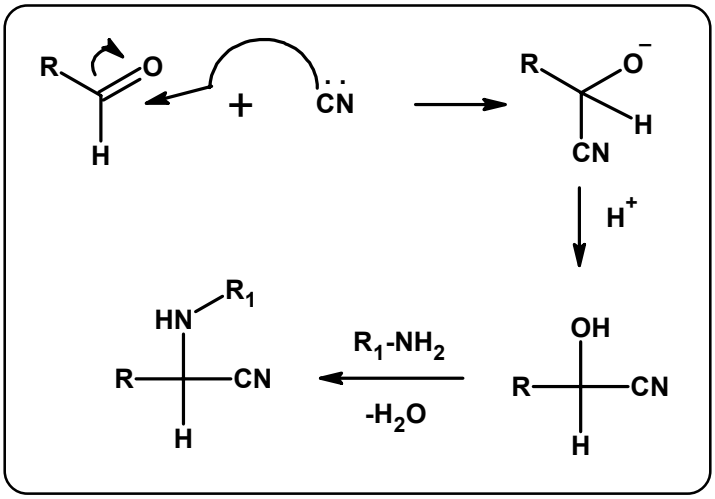
4. Mohanakrishna A. K. and co-workers[374] have synthesised nitrile derivatives of type (III) is as under.



(III)

MECHANISM

The mechanism of nitrle formation is shown as under.



Reaction between CN and aldehyde is a type of nucleophilic substitution reaction. From the above reaction, it can be seen that a nucleophile (CN) attacks on the carbonyl carbon of aldehyde and yields cyanohydrin which reacts with amine to yield nitrile derivatives.

THERAPEUTIC IMPORTANCE

They shows various therapeutic activities which are described as under.

(a) Antiarrythemic[375]

(b) Pesticidal[376]

(c) Herbicidal[377]

(d) Fungicidal[378]

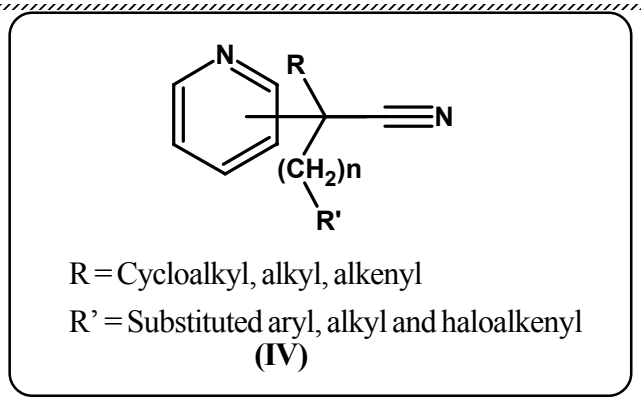
(e) Antihypertensive[379]

(f) Antihypoxic[380]

(g) Antiinflammatory[381]

(h) Antimicrobial[382]

Nitriles with fused pyridine ring were reported as ulcer inhibitor[383]. Kobayashi et. al.[384] have synthesised new derivatives of nitriles. M. C. Dougal[385] have synthesised nitriles and studied their pharmacological activities. Lai Hio Kiong and co-workers6[386] have reported nitriles (IV) showing fungicidal activity.

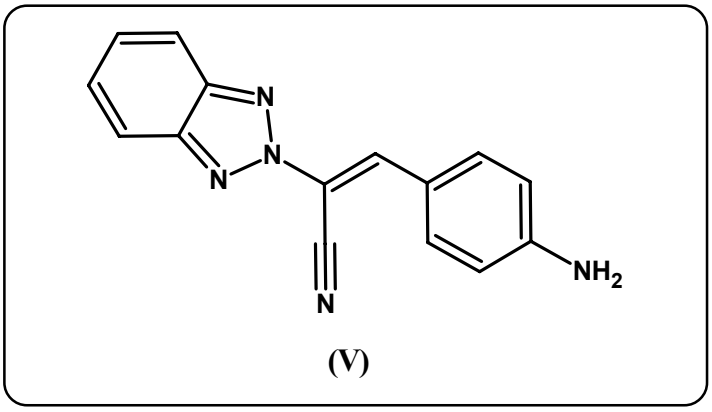


R = Cycloalkyl, alkyl, alkenyl

R' = Substituted aryl, alkyl and haloalkenyl

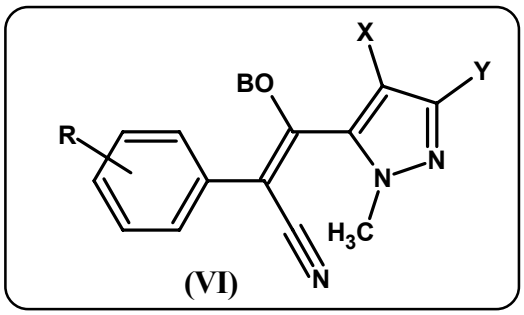
(IV)

Yogihara and co-workers[387] have documented antimicrobial and antiinflammatory activity of nitriles. Nosyrava et. al.[388] have formulated novel nitriles possessing muscle relaxant activity. Valmajer Juliya et. al.[289] have tested some new nitriles as anticonvulsant agent.Shibata Yasushi and co-workers[390] have reported nitriles as insecticides. Parlo Sanna et. al.[391] have synthesised nitriles (V) and screened for their antitubercular activity.



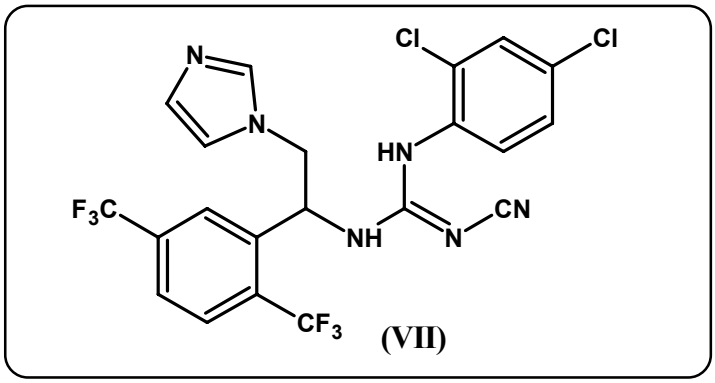
(V)

Iwanowicz E. J. et. al.[392] have synthesised nitriles and found preventing and treating IMPDH associated disorders, such as transplant rejection and autoimmune disease. Ian J. S. Fairlamb et. al.[393] have prepared nitrile derivatives and tested for their antimicrobial activity. Murakkami Hiroshi et. al.[394] have investigated some new nitriles and studied their pesticidal and marin antifouling activity.



(VI)

Cyanoguanidine derivatives (VII) have been synthesised and reported as inhibitors of mitochondrial F, FO, ATPase by A. Karnails et al.[395] Nurolaini Kifli et. al.[396] have discovered nitriles and reported their antiviral activity.

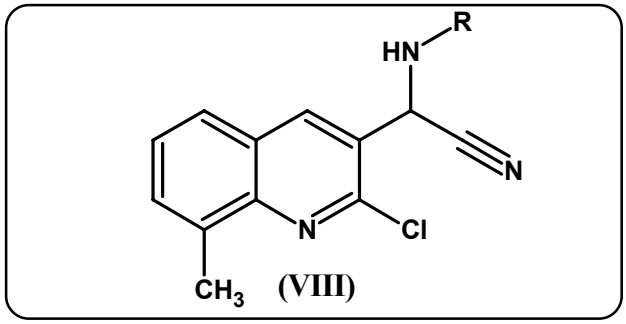


(VII)

Recently, Marion Nipper et. al.[397] have prepared nitriles useful as antimicrobial agent. Miroslav Otmar et. al.[398] have formulated nitriles possessing antiproliferative activity. S. Srinivasan et. al.[399] have investigated nitriles which showed antimicrobial activity. Olivier Nicolas and co-workers[400] have discovered nitrile derivatives possessing moderate antimalarial activity. Guohua Zhao et. al.[401] have reported Diprolyl nitriles as potent dipeptidyl peptidase IV inhibitors. Jon Bondebjerg and co-workers[402] have identified a potent and selective inhibitor of human dipeptidyl peptidase I by using a dipeptide nitrile scaffold.

CONTRIBUTION FROM OUR LABORATORY

F. M. Bharmal and H. H. Parekh[403] have synthesised newer acetonitriles (VIII) bearing quinoline moiety and tested them as antimicrobial agent.



(VIII)

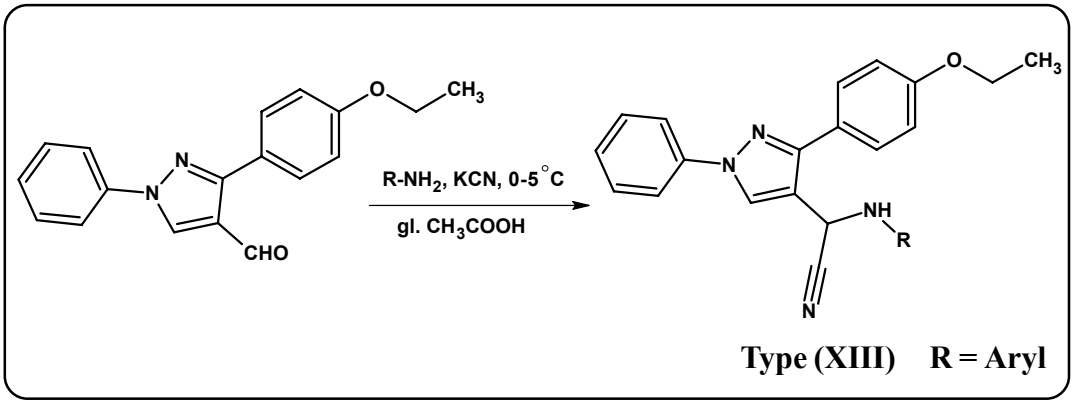
Looking to the interesting properties of nitriles, we have synthesised some new nitriles, which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ACETONITRILES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF a-ARYLAMINO-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ACETONITRILES

In view of therapeutic activities of nitriles, it was contemplated to synthesise some new nitriles in search of agents possessing higher biological activity. Nitriles of type (XIII) have been synthesised by the reaction of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole with different aromatic amines in the presence of potassium cyanide and glacial acetic acid at 0-5^{0}C.

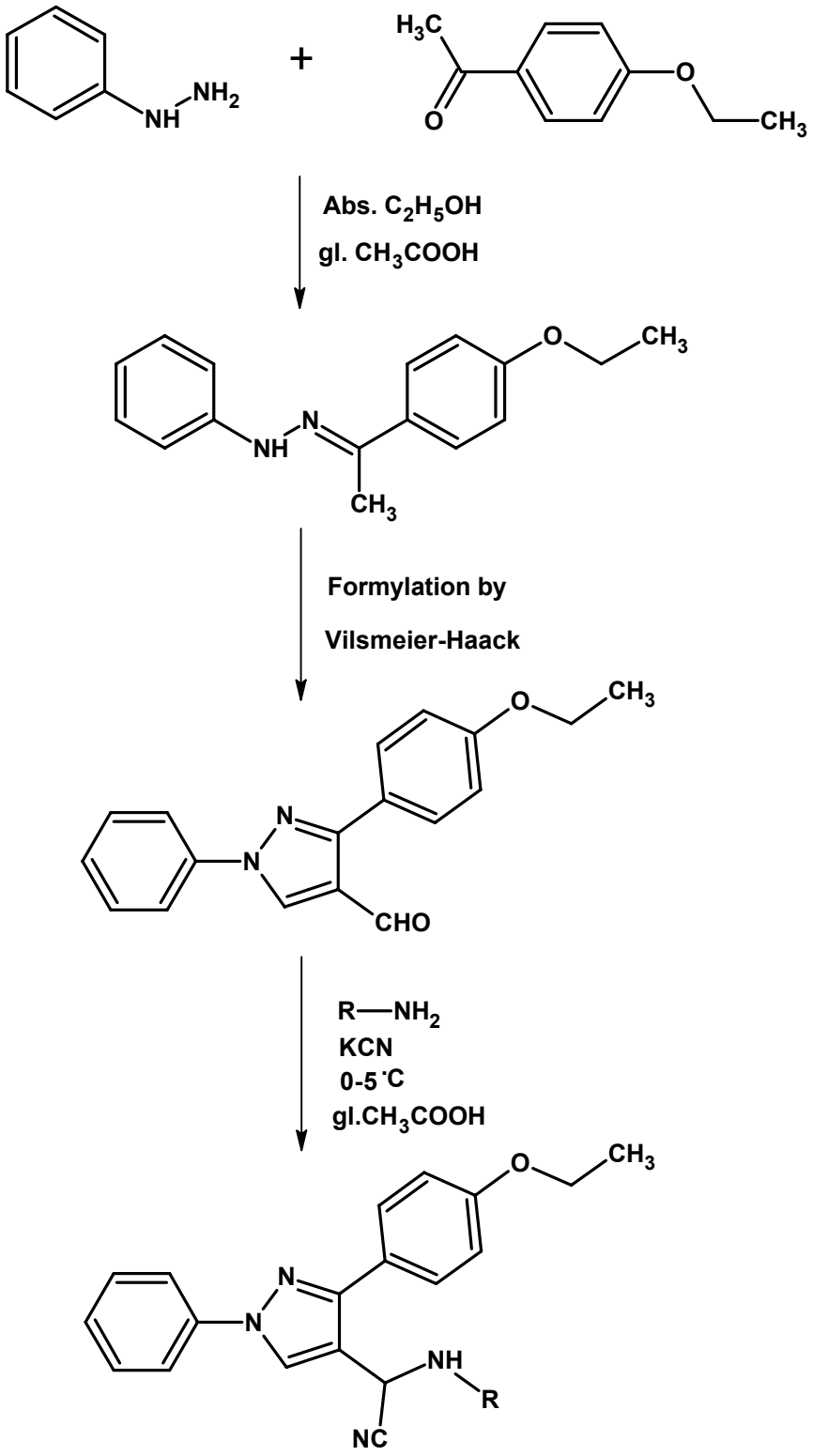


Type (XIII) R = Aryl

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

REACTION SCHEME



Type - (XIII) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF a-ARYLAMINO-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ACETONITRILES

(A) Synthesis of *p*-Ethoxyphenylhydrazone[111]

See [A] Part-I, Section-I (A).

(B) Synthesis of 1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole[112]

See [A] Part-I, Section-I (B).

(C) Synthesis of a-*p*-Bromophenylamino-(1',N-phenyl-3'-*p*-ethoxyphenyl pyrazol-4'-yl)acetonitrile

1,N-Phenyl-3-*p*-ethoxyphenyl-4-formyl pyrazole (2.92 g, 0.01M) dissolved in ethanol (25ml) was added to potassium cyanide (0.64g, 0.01M) dissolved in water (15 ml) followed by addition of glacial acetic acid (12 ml). The contents were then stirred for 5 minutes to form cyanohydrin at 0^{o}C. *p*-Bromoaniline (1.72g, 0.01M) dissolved in methanol was added to the reaction mixture, contents were stirred at room temperature for 24 hrs. The content was poured onto curshed ice. The solid product was filtered and crystallised from ethanol. Yield 68%, m.p. 168^{o}C ($C_{25}H_{21}BrN_4O$; Required : C, 63.43; H, 4.47; N, 11.84; Found : C, 63.38; H, 4.42; N, 11.79 %).

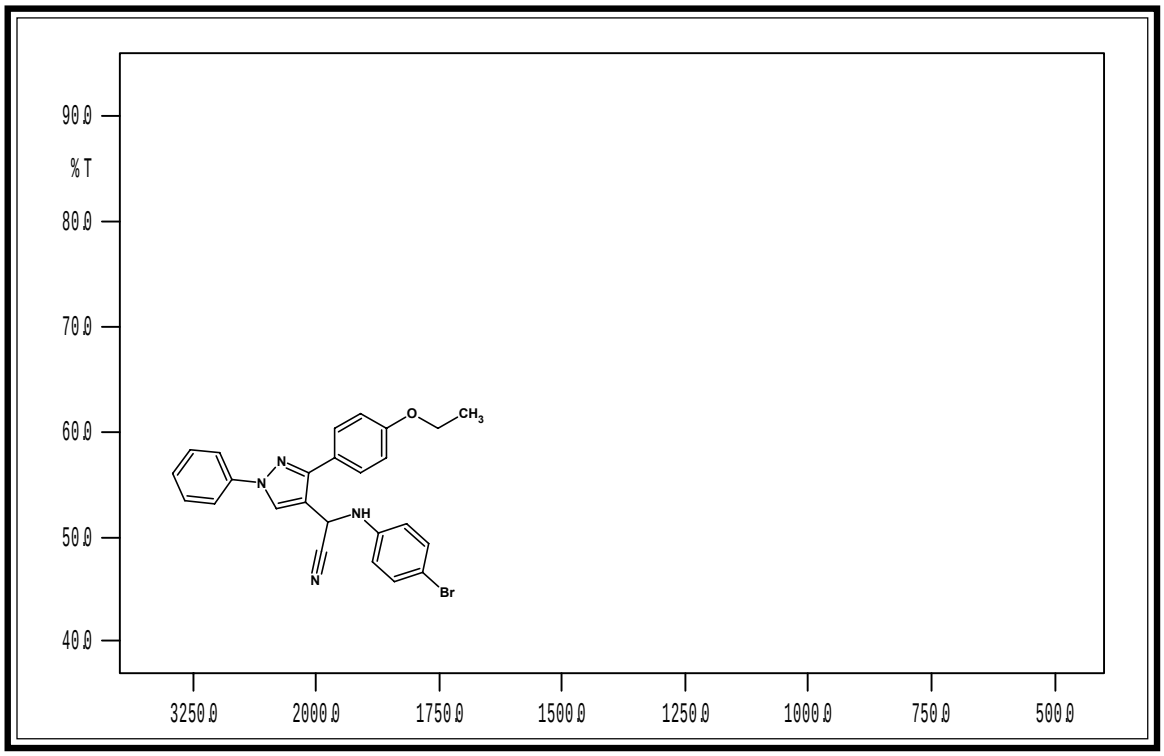
TLC solvent system : Acetone : Benzene (1 : 9).

Similarly other substituted nitriles have been prepared. The physical data are recorded in Table No. 13.

(E) Antimicrobial activity of a-arylamino-(1',N-phenyl-3'-*p*-ethoxyphenyl-pyrazol-4'-yl)-acetonitriles

Antimicrobial testing was carried out as described in [A] Part-I, section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 13.

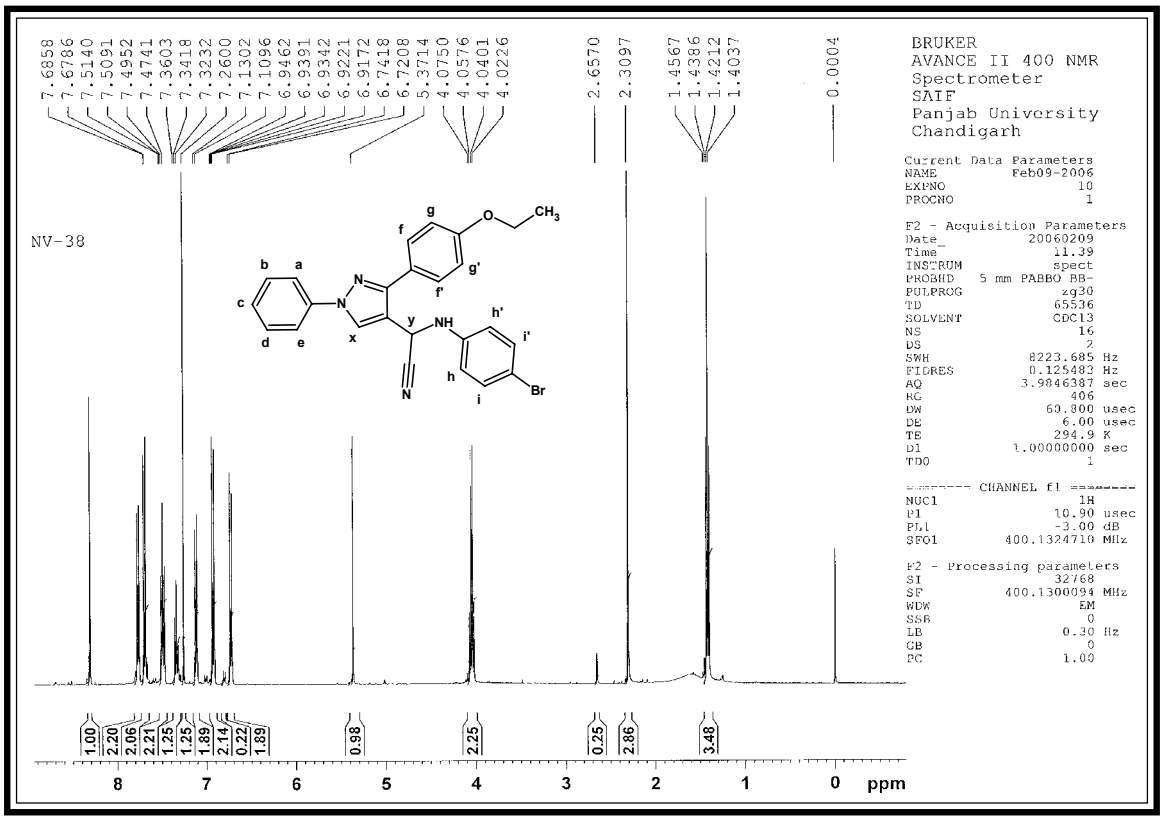
IR SPECTRAL STUDY OF a-*p*-BROMOPHENYLAMINO-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)ACETONITRILE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2916	2975-2950	413
$-CH_3$	C-H str. (sym.)	2854	2880-2860	
	C-H i.p.def. (asym.)	1448	1470-1435	
Aromatic	C-H str.	3060	3080-3030	
	C=C str.	1502	1585-1480	414
	C-H i.p. def.	1064	1125-1090	
	C-H o.o.p. def	837	835-810	
Pyrazole	C=N str.	1595	1630-1590	415
moiety	C-N str.	1159	1230-1020	
	C-Br str.	759	600-800	413
Ether	C-O-C str. (asym.)	1232	1275-1200	414
	C-O-C str. (sym.)	1064 (overlapped)	1075-1020	
Nitrile	$C^{O}N$ str.	2216	2240-2220	420
	N-H str.	3355	3350-3200	

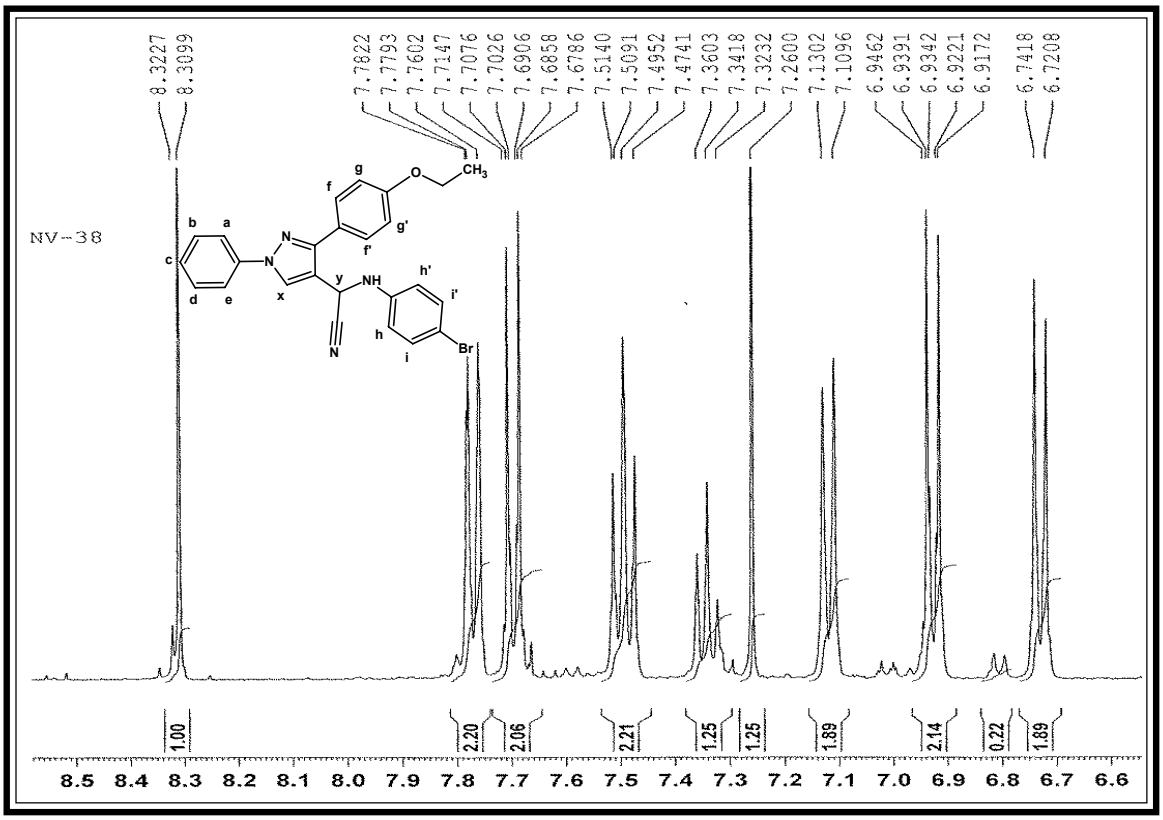
PMR SPECTRAL STUDY OF a-*p*-BROMOPHENYLAMINO-(1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)ACETONITRILE

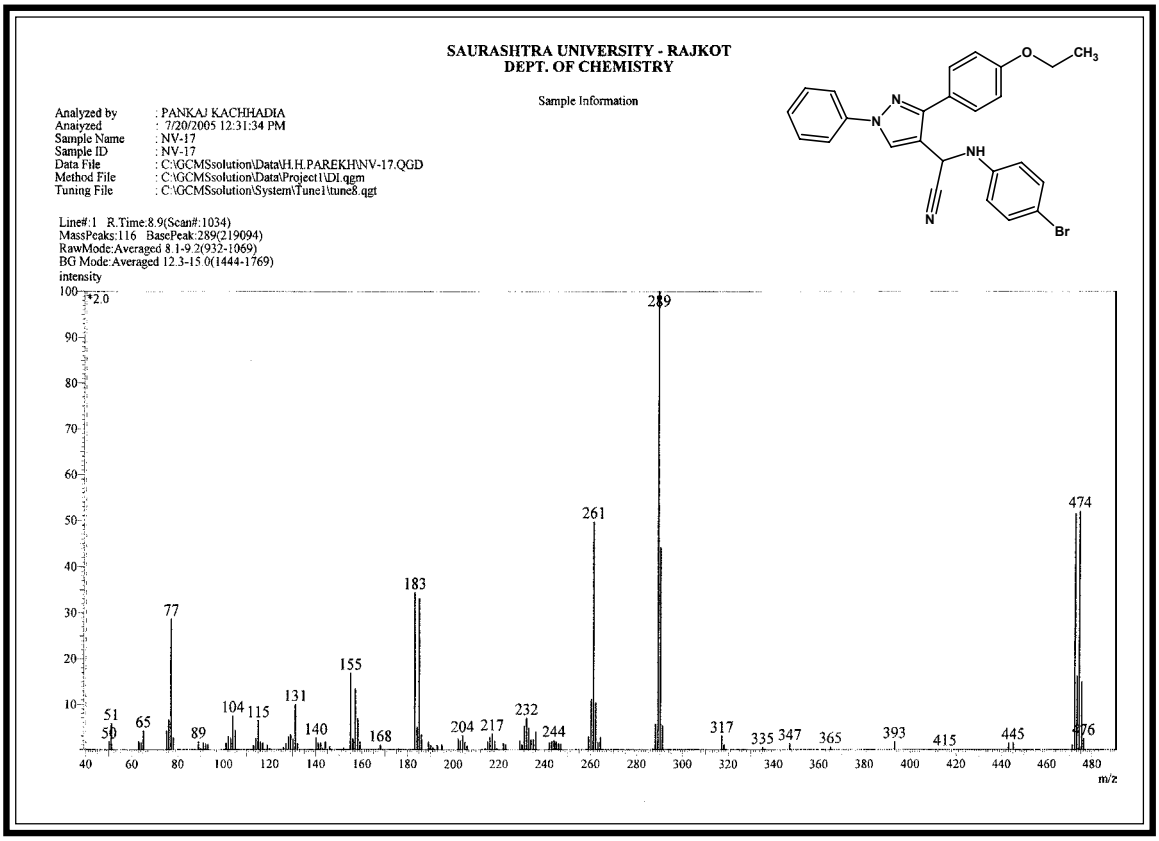


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (d ppm)	Relative No.	Multiplicity	Inference	J Value In Hz
1.	1.40-1.45	3H	triplet	$-OCH_2\underline{CH}_3$	J_{CH_3}=6.9
2.	4.02-4.07	2H	quartret	$-O\underline{CH}_2CH_3$	J_{CH_2}=7.0
3.	5.37	1H	singlet	CH_y	-
4.	6.72-6.74	2H	doublet	Ar-$H_{gg'}$	J_{gf}=8.4
5.	6.91-6.93	2H	doublet	Ar-$H_{hh'}$	J_{hi}=8.7
6.	7.10-7.13	2H	doublet	Ar-H_{ae}	J_{ab}=8.2
7.	7.23-7.36	1H	triplet	Ar-H_c	-
8.	7.47-7.51	2H	triplet	Ar-H_{bd}	-
9.	7.68-7.70	2H	doublet	Ar-$H_{ii'}$	J_{ih}=8.7
10.	7.76-7.78	2H	doublet	Ar-$H_{ff'}$	J_{fg}=8.4
11.	8.30	1H	singlet	CH_x	-

EXPANDED AROMATIC REGION





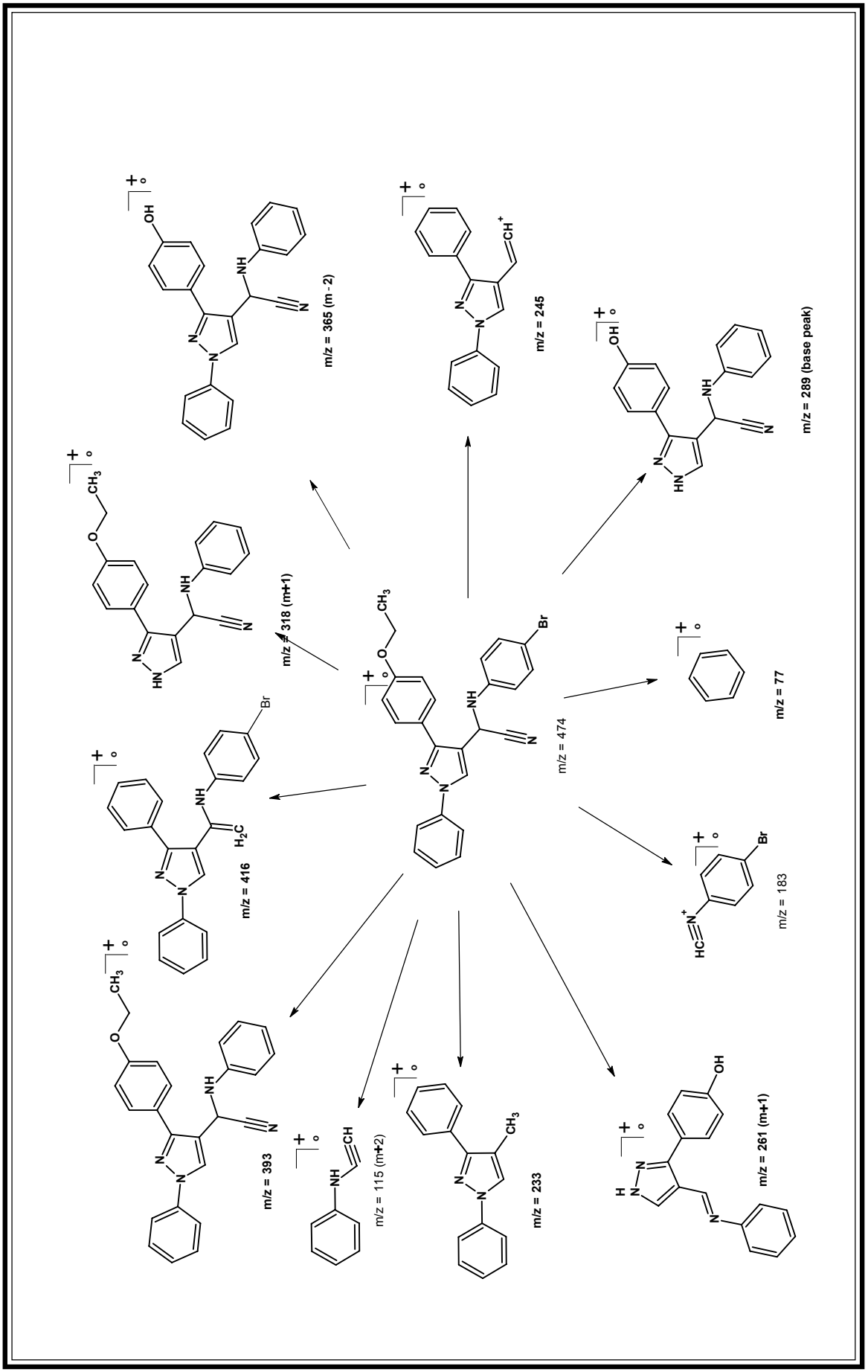
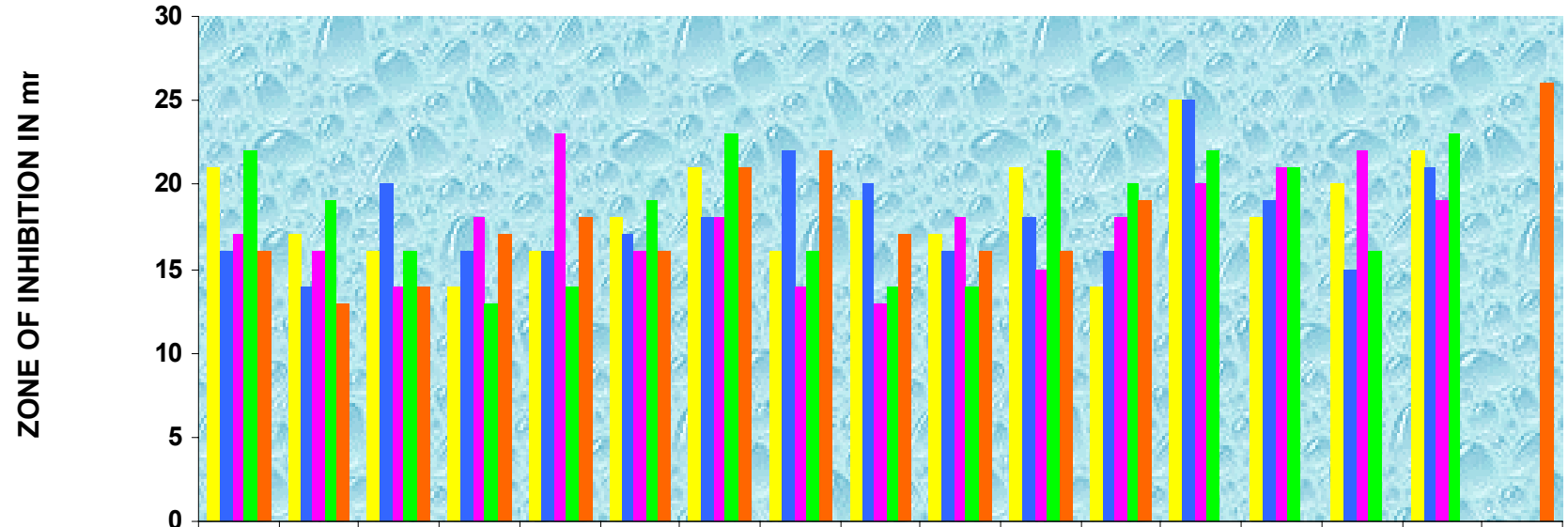

m/z = 474
m/z = 365 (m - 2)
m/z = 245
m/z = 289 (base peak)
m/z = 318 (m+1)
m/z = 77
m/z = 416
m/z = 183
m/z = 393
m/z = 115 (m+2)
m/z = 233
m/z = 261 (m+1)

TABLE-13 : PHYSICAL CONSTANTS OF *a*-ARYLAMINO-(1',N PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ACETONITRILES

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Rf* Value	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8	9
13a	C_6H_5-	$C_{25}H_{22}N_4O$	394	169	0.56	64	14.20	14.15
13b	4-Cl-C_6H_4-	$C_{25}H_{21}ClN_4O$	428.5	160	0.52	69	13.06	13.01
13c	4-CH_3-C_6H_4-	$C_{26}H_{24}N_4O$	408	174	0.56	55	12.09	12.04
13d	4-Br-C_6H_4-	$C_{25}H_{21}BrN_4O$	473	168	0.63	68	11.84	11.79
13e	4-F-C_6H_4-	$C_{25}H_{21}FN_4O$	412	165	0.64	60	13.58	13.54
13f	3-Cl,4-F-C_6H_3-	$C_{25}H_{20}ClFN_4O$	446.5	144	0.53	70	12.54	12.49
13g	2-OCH_3-C_6H_4-	$C_{26}H_{24}N_4O_2$	424	135	0.54	72	13.20	13.15
13h	4-OCH_3-C_6H_4-	$C_{26}H_{24}N_4O_2$	424	146	0.52	58	13.20	13.14
13i	2-CH_3-C_6H_4-	$C_{26}H_{24}N_4O$	408	149	0.50	64	13.72	13.66
13j	3,4-$(Cl)_2$-C_6H_3-	$C_{25}H_{20}Cl_2N_4O$	463	198	0.53	64	13.72	13.67
13k	2-NO_2-C_6H_4-	$C_{25}H_{21}N_5O_3$	439	155	0.73	72	15.94	15.90
13l	4-NO_2-C_6H_4-	$C_{25}H_{21}N_5O_3$	439	168	0.61	63	15.94	15.89

*TLC Solvent System : Acetone : Benzene (1 : 9)

GRAPHICAL CHART NO. 13 : ANTIMICROBIAL ACTIVITY OF *a*-ARYLAMINO-(1',N PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL)-ACETONITRILES



	13a	13b	13c	13d	13e	13f	13g	13h	13i	13j	13k	13l	Amoxicillin	Benzoylpenicilli	Ciprofloxacin	Erythromycin	Greseofulvin
B. coccus	21	17	16	14	16	18	21	16	19	17	21	14	25	18	20	22	0
S. aureus	16	14	20	16	16	17	18	22	20	16	18	16	25	19	15	21	0
E.Aerogenes	17	16	14	18	23	16	18	14	13	18	15	18	20	21	22	19	0
P.aeruginosa	22	19	16	13	14	19	23	16	14	14	22	20	22	21	16	23	0
A. niger	16	13	14	17	18	16	21	22	17	16	16	19	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

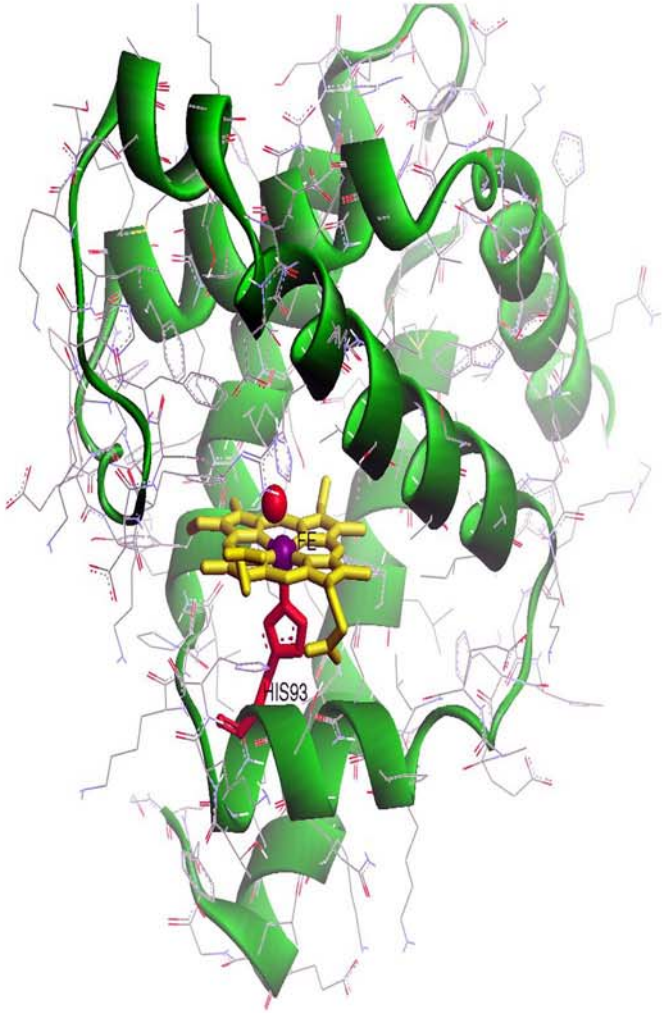
It has been concluded from the experimental data that the compounds bearing R=phenyl, 2-methoxyphenyl and 2-nitrophenyl have displayed good activity against ***B.coccus***. The compounds bearing R= 4-methoxyphenyl have shown considerable activity against ***S.aureus***.

In case of Gram negative bacterial strains, all the compounds were inactive against ***Aerogenes*** except the compound bearing R=4-fluorophenyl. While the compounds bearing R=phenyl, 2-methoxyphenyl and 4-nitrophenyl showed significant activity against ***Pseudomonas***.

ANTIFUNGAL ACTIVITY

All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=2-methoxyphenyl and 4-methoxyphenyl displayed highest activity against ***A.niger.***

The antibacterial activity was compared with standard drug viz.amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.



{B}

STUDIES ON MICROWAVE INDUCED ORGANIC REACTION ENHANCEMENT

INTRODUCTION

Microwave radiation is a descriptive term used to identify electromagnetic waves in frequency spectrum ranging from 1 Giga Hertz (10 Hz) to 30 Giga Hertz. In order to avoid interfering with radar and telecommunication activites which operate within this region, most domestic and commercial microwave instruments operate at 2.45 GHz. These waves represents several interesting and unusual features which not found in other portions of the electromagnetic spectrum. These features makes "microwaves" uniquely suitable for several useful applications like industrial, scientific, domestic and medicinal.

The heating effect utilised in microwave assisted organic trasformations is mainly due to the dielectric polarisation, although conduction losses can also be important particularly at higher temperatures. Whilst the polaristability of a molecule (determined by the Debye equation) is the sum of a number of contributions only dipolar and interfacial polarisation are important to heating effects associated with microwave irradiation. These include the preparation of sample for analysis[404], application to waste treatment[405], polymer technology[406], drug release/targeting[407,408], and chemistry[409-411].

Microwave induced organic reaction enhancement chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis, important features of this technique are easy access to very high temperature , good control over energy input in a reation and rapid synthesis of organic compounds. The advantages of microwave induced organic reaction enhancement chemistry include requirement of simple, in expensive instrument, lesser quantites of solvent and eco-friendly technology.

Microwave heating is distinguished primarily by being radiant process. It's relationship to ordinary heat is of much interest. Regular heat rays differ in frequency and properties. In the conventional method, heat is generated by molecular collosions which accomplish the energy transfer, while microwave cause heating through the absorption of energy quanta.

Those molecule having dipole moment when submitted to an electric field, they become aligned. If this field oscillates, the orienatation of molecules, in phase with the electrical field exacitaiton, cause intense internal heating , upto 1000˚C per second, when powerful waves are used.

The main interests can thus be listed as the rapid trasfer of energy into the bulk of the reaction mixture, without interia since only the product is heated and the ease of utiliation. Furthermore, as the depth of penetration in materals is of the same order of magnitude as the wavelength, microwaves interect with substancess of appreciable thickness (about 10 cm.)

The interfacial polarisation, the Maxwell-Wagner effect, may also contribute to the heating effect when the conducting particles are in contact with a non conducting medium. eg. in heterogenous reactions. It is particularly convenient that qualitatively, the larger the dielectric constant, the greater the coupling with microwaves. Thus, solvents such as water, methanol, DMF, ethylacetate, acetone and R-spirit are all heated when irradiated with microwaves. Non-polar solvents like carbon tetra chloride, toluene, xylene, benzene do not couple and therefore do not heat with microwave irradiation.

Generally, commercial microwave oven is being used in the chemical laboratory of a frequency of 2450 MHz. The first application of microwave ovens in organic synthesis began very recently. By the first exeperiments of Gedye and Giguere, the evidence for dramatic acceleration in some classical organic reaction, esatblished and these were ascribed to temperature and pressure effects, when performed in closed teflon vessels. The reaction can be carried out in teflon, polystyrene and glass vessels since these are transparent to microwaves. Microwave irradiation has also been applied for carrying out reactions in open vessels, using organic solvents. The relatively low cost of modern domestic microwave ovens makes them reasonably readily available to academic and industrial chemists.

These experiments sometimes needs solvents which faces some problems with no safe operation appeared and sometimes explosion results. Therefore, to solve these problems solvent free reaction has been developed and to facilitate the scale-up of preparative runs. Recently, reaction under dry condition using inorganic

reagents are ganging more attention because of their enhance selectivity and milder conditions than those associated with conventional homogenous reaction procedures.it should,be noted that some of inorganic additives reach temperature in excess of 1000˚C very rapidly and decomposition of materials may be problematic, therefore some precautions regarding superheating and associated fire hazardes or explosions are taken.

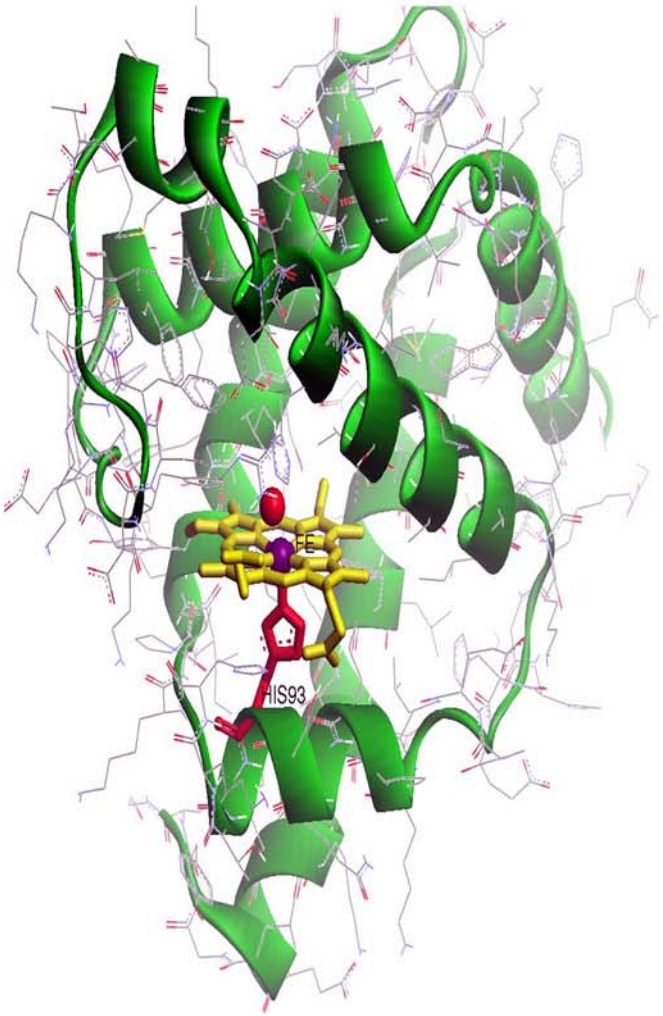
Detail review on "Microwave Assisted Reaction" by S. Caddick[412] involves variety of unusual chemical reactions like,

1. Aromatic substitution reaction
2. Alkane synthesis
3. Oximes
4. Alkylation reaction
5. Decarboxylation
6. Radical reactions
7. Catalytic transfer hydrogenation
8. Cyclisation reactions
9. Pericyclic reactions
10. Alkane functionalisation

Successfully loading to the pathway from non traditional approach to the experimental setup of organic reactions, the concept of "Microwave Induced Organic Reaction Enhancement" (MORE) chemistry has been utilised for rapid and efficient synthesis of pyrazolines and methoxy pyridines bearing pyrazole moiety which is described as under.

SECTION-I : MICROWAVE ENHANCED SYNTHESIS OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL]-PYRAZOLINES

SECTION-III : MICROWAVE ENHANCED SYNTHESIS OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL]-6-ARYL PYRIDINES



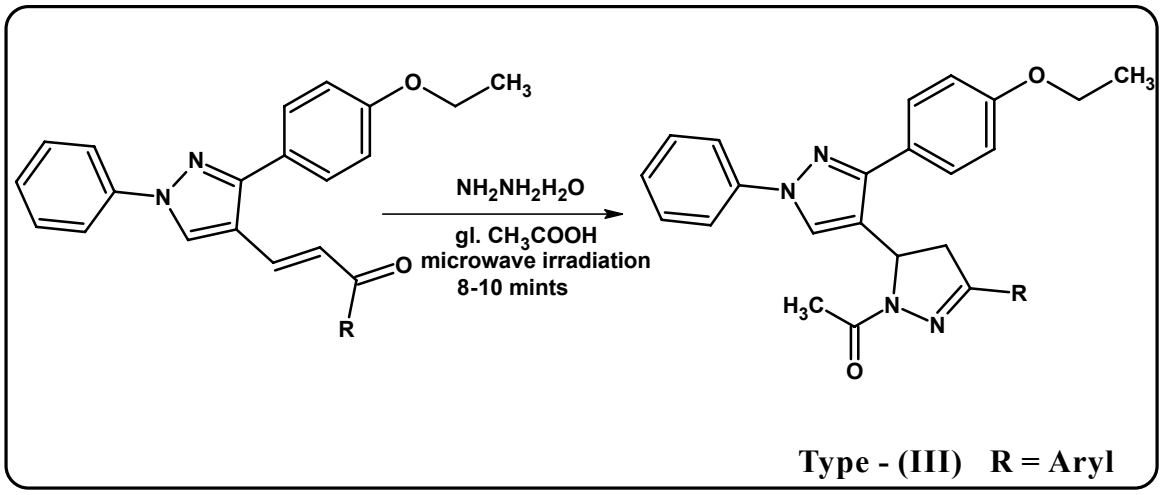
PART-I

STUDIES ON ACETYLPYRAZOLINES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL)-PYRAZOL-4'-YL]-PYRAZOLINES BY MICROWAVE ENHANCED SYNTHESIS

As microwave used to create effect in organic synthesis, the "in situ" generation of heat is very efficient and can be used to significantly reduce reaction times of synthetically useful organic transformations. Thus microwave assisted organic synthesis has advantages over conventional techonology. We have synthesised pyrazoline derivatives of type (III) by the reaction of chalcone with hydrazine hydrate in glacial acetic acid under microwave irradiation as cited under.



Type - (III) R = Aryl

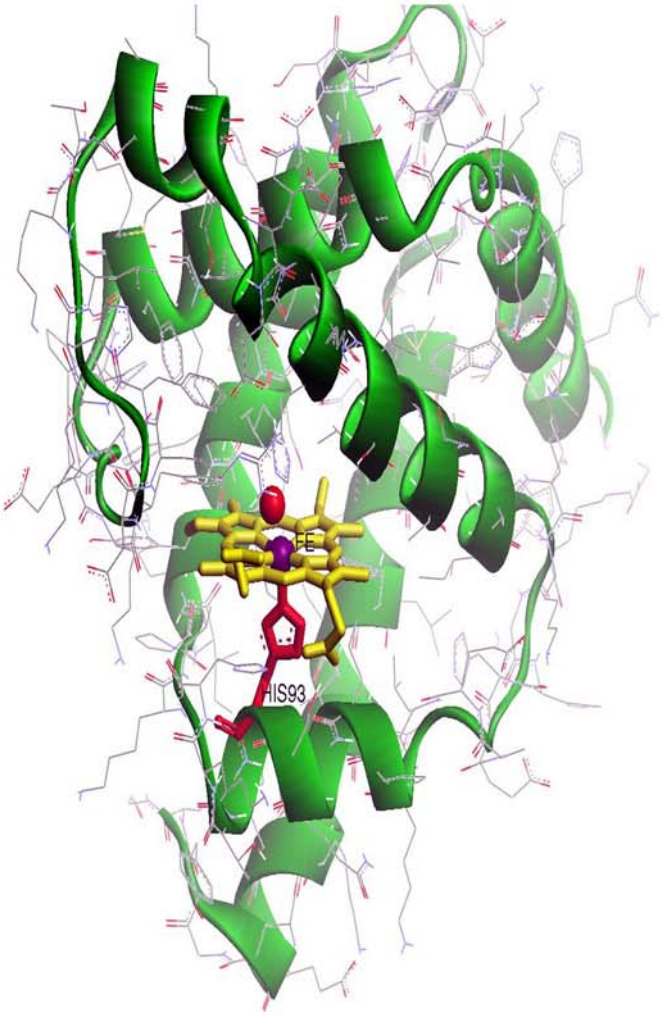
The constitution of the synthesised products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

The compounds of type (III) have been already synthesised using conventonal method as reported earlier in Part-I, section-III (D).

Q. Pro-M Microwave Oven, Questron Technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period have been cited in Table No. 3a.

TABLE NO. 3a : COMPARISON OF CONVENTIONAL METHOD AND MICROWAVE INDUCED SYNTHESIS OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-*p*-ETHOXYPHENYL-PYRAZOL-4'-YL]-PYRAZOLINES

Comp. No.	R	Thermal		Microwave		M. P. ^{o}C
		Reaction Period (hrs.)	Yield %	Reaction Period (min.)	Yield %	
2a	C_6H_5-	09	59	07	69	168
2b	4-NH_2-C_6H_4-	08	60	08	74	121
2c	4-Cl-C_6H_4-	08	70	10	77	087
2d	4-Br-C_6H_4-	10	72	10	65	093
2e	4-F-C_6H_4-	09	64	09	70	201
2f	2-OH-C_6H_4-	08	58	10	70	185
2g	4-OH-C_6H_4-	10	54	11	73	123
2h	4-OCH_3-C_6H_4-	10	76	10	68	099
2i	4-CH_3-C_6H_4-	11	51	08	65	154
2j	3-NO_2-C_6H_4-	08	74	07	78	111
2k	4-NO_2-C_6H_4-	09	68	08	70	095
2l	2-C_4H_3S-	10	61	10	73	183

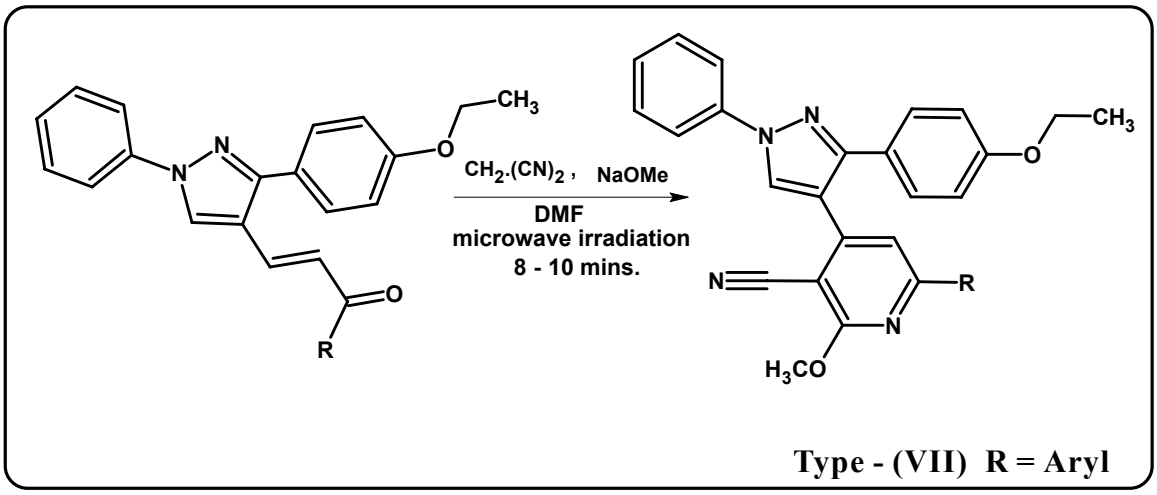


PART-II

STUDIES ON CYANOPYRIDINES

SECTION - II

As a part of our research programme towards the non traditinal approach to the experimental set up of organic reactions, the concept of "Microwave induced Organic Reaction Enhancement" (MORE) chemistry has been utilised for rapid and efficient synthesis of cyanopyridine derivatives of type (VII).The synthesis was carried out by the condensation of chalcones of type (I) with malononitrile in presence of sodium methoxide under microwave irradiation as cited under.



Type - (VII) R = Aryl

The constitution of the synthesised products have been characterized by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

The compounds of type (VII) have been already synthesised using conventonal method as reported earlier in Part-VI, section-I (D).

Q. Pro-M Microwave Oven, Questron Technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period have been cited in Table No. 11a.

TABLE NO. 11a : COMPARISON OF CONVENTIONAL METHOD AND MICROWAVE INDUCED SYNTHESIS OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-(*p*-ETHOXYPHENYL) PYRAZOL-4'-YL]-6-ARYL PYRIDINES

Comp. No.	R	Thermal		Microwave		M. P. ^{o}C
		Reaction Period (hrs.)	Yield %	Reaction Period (min.)	Yield %	
11a	C_6H_5-	09	65	09	70	154
11b	4-OCH_3-C_6H_4-	10	59	10	69	196
11c	4-CH_3-C_6H_4-	08	70	09	75	244
11d	4-Cl-C_6H_4-	09	63	10	68	186
11e	4-F-C_6H_4-	08	60	10	65	201
11f	4-Br-C_6H_4-	08	62	10	68	168
11g	4-OH-C_6H_4-	10	69	10	72	199
11h	2-OH-C_6H_4-	10	70	08	75	180
11i	4-NO_2-C_6H_4-	11	59	10	67	147
11j	3-NO_2-C_6H_4-	10	60	10	64	150
11k	2-C_4H_3-	10	63	09	69	178
11l	4-NH_2-C_6H_4-	08	64	08	70	183

CONCLUSION

We have demonstrated a rapid and general synthesis of acetyl pyrazolines and methoxy pyridines using a microwave oven. Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformation in minutes, instead of hours. Consequently, reactions exhibit cleaner products and more facile work-up procedures. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis.Moreover, can lead to improve isolated yields compared to conventional technology.

REFERENCES

REFERENCES

1. Knorr and Blank;
   Ber., **18,** 311 (1885).
2. Knorr;
   Ger. Pat., **26**, 429 (1983) [Friedander, 1, 208].
3. Knorr;
   Ber., **16,** 2597 (1887)
4. R. C. Boruah;A. Saikia; M. G. Barthakur; M. Borthakur; C. J. Saikia; U. Bora;
   Tetrahedron Lett., *Vol*. **47**, No.1 pp. 43-46 (2006)
5. M. J. Kurth;Y. F. Suen; H. Hope; M. H. Nantz; M. J. Haddadin;
   J. Org. Chem., 2005, **70**(21), 8488-8471
6. J. J. Talley, Shikorski, A. James, G. Matthew, C. Jaffreys;
   PCT. Int. Appl. WO **96** 38, 418 (Cl. C07D231/12); *Chem. Abstr.,* **126,** 104081p (1997).
7. John Talley, Thomas Penning, Paul Collins, Donald Rogier;
   U. S. US **5,** 760, 068 (Cl. 514-403; A61K31/415); *Chem. Abstr.,* **129**, 54367q (1998).
8. K. Yasuyuki, K. Toshuki, N. Makato, M. Yukiaki;
   Jpn. Kokai Tokkyo Koho JP **08,** 311, 036; *Chem. Abstr.,* **126,** 89367r (1997).
9. A. Ananta Narayan, C. Michale, G. Lifeng, G. J. Hanson, R. A. Partis, M. A. Stealey;
   PCT Int Appl. WO **98** 52, 937 (Cl. C07 D401/00); *Chem. Abstr.,* **130,** 25069v (1999).
10. M. Manfred. L. Hans-Joachim, V. Klaus;
    Ger. Otten DE **19,** 521, 822 (Cl. C07D 231/38); *Chem. Abstr.,* **126,** 117969j (1997).
11. W. Kulsuaki, G. Takuya;
    PCT Int. Appl. WO 00 09, 500 (Cl. CO7D409/00); *Chem. Abstr.,* **132;** 180518x (2000).
12. L. Paolo, M. Stefano, S. Daniele, P. Alssandra;
    PCT. Int. Appl. WO **96,** 40, 704 (Cl. C07419/04), 19 Dec. 1996; *Chem. Abstr.,* **126,** 118161b (1997).
13. S. D. Bhardwaj, V. S. Jolly;
    Oriental J. Chem., 1996, **12(2),** 185-187 (Eng.); *Chem. Abstr.,* **126,** 1442174, (1997).
14. L. Paolo, M. Stefano, S. Daniele, P. Alssandra;
    PCT. Int. Appl. WO **96,** 40, 704 (Cl. C07419/04), 19 Dec. 1996; *Chem. Abstr.,* **126,** 118161b (1997).
15. T.Siddall, B.Lyman, G.Zaltan, Gail;
    PCT Int. Appl. WO **98,** 52, 926; *Chem. Abstr.,* **130,** 25068u (1999).
16. Lyman Thomas, Zoltan Benko, Maric Gail;
    PCT Int. Appl. WO **98,** 52, 926; *Chem. Abstr.,* **131,** 35132w (1999).

17. Genin J. Michael; Biles, Carolyn, J.Keiser;
J. Med. Chem., **43,** 1034-1040 (2000).

18. K. Jansen, G. Reinhald, S. Otto, H. Bernhard;
Ger. Offen. DE **3,** 711, 928 (Cl. C07D 231/18); *Chem. Abstr.,* **110,** (1989).

19. S. Shinzo, K. Seigo, I. Mikio, W. Hiroyuki, T. Kenji;
Jpn. Kokai Tokkyo Koho JP **63,** 264, 584 [88, 264, 584] (Cl. C07D 413112); *Chem. Abstr.,* **110,** 1732244 (1989).

20. G. Reinhald, S. Otto. S. Joerg, K. Erich;
Ger. Offen., DE **3,** 712, 425 (Cl. C07D 231/40); *Chem. Abstr.,* **110,** 173394x (1989).

21. K. Nakamura K. Okumura, A. Takashi, K. Takeshi, Y. Hirofumi;
PCT. Int. Appl. WO **99,** 15, 505; *Chem. Abstr.,* **130,** 252354c (1999).

22. K. Nakamura, T. Tadashi, O. Takashi;
PCT Int. Appl. WO **99** 25, 695; *Chem. Abstr.,* **131,** 5254u, (1999).

23. Banks Bernard Joseph, Wehster Richard Andrew Bentley;
Eur. Pat. Appl. EP 759, 071; *Chem. Abstr.,* **131,** 351325w, (1999).

24. G..Menozzi ,L. Mosti ., P.Schenone , M.D.Amico ,C. Falzarano and F.Rossi ;
Farmaco, **48(4)**, 539-549 (1993).

25. Giuseppe Daidone, Benedetta Maggio, Salvatore Plescia, Demetrio Raffa, Domenico Schillaci, Onofrio Migliara, Antonella Caruso and Maria Amico-Roxas;
IL Farmaco, **53(5)**, 350-356 (1998).

26. E. Akio, O. Satory;
PCT Int. Appl. wo **98,** 32, 739 (Cl. C07D231/12); *Chem. Abstr.,* **128,** 154079f (1998).

27. Laborde Edgardo, O.Villar Hugo ;
PCT Int. Appl. WO **02** 64135 (Cl. A61K 31/41) (2002); *Chem. Abstr.,* **137,** 169526j (2002).

28. Andrew Thurkaub, Zhang Xiaoyan, Hexiashu, Chliger Robert;
PCT Int. Appl. WO **02** 49993 (Cl. C07D) (2002); *Chem. Abstr.,* **137,** 78952d (2002).

29. Nagaaki Sato; Toshiyaki Takahash, Takunobu, Shibata;
J. Med. Chem., **46,** 666 (2003).

30. G.M.B.Merck Patent Hi Yamanonch Pharm CO;
Ger. Offen DE **10** 149370 (Cl. CO7D403/14) (2003); *Chem. Abstr.,* **138**, 304276r (2003).

31. L. S.David , G.David Brummell et al.;
J. Med. Chem., **44,** 78-93 (2001).

32. T. Van Herk, J. Brussec, A. M. C. H. Vanden, Nienwendisk;
J. Med. Chem., **46,** 3945 (2003).

33. Barber Christopher, Gordon Maw, Graham Nigel;
Eur. Pat. Appl. EP 1241170 (Cl. C07D 487/14) (2002); *Chem. Abstr.,* **137,** 232664v (2002).

34. R. N.Atkinson , M. F.Gross ;
PCT Int. Appl. WO **03** 37,274 (Cl. A Cl. K) (2003); *Chem. Abstr.,* **138,** 368888z (2003).

35. Gellibert Francoise, Jeanne Glaxo;
PCT Int Appl. WO **02** 62781 (Cl. CO7D401/14); *Chem. Abstr.,* **137,** 169514d (2002).

36. G. Mamalo, D. Zampieri, V. Fallagiani, V. L. Banfi;
Chem. Abstr., **136,** 200135m (2002).

37. R. Y. Huang, K. Illenbogen, A. John;
Org. Lett. 2000, **2(18),** 283583g (Eng); *Chem. Abstr.,* **132,** 207842m (2000).

38. C. Vittoria, C. Daniely. V. Flavia, C. Lucia;
J. Med. Chem., 2000, **43(16);** 3118-3124 (Eng.); *Chem. Abstr.,* **133,** 281723q (2000).

39. U. Schindler, K. Schoena Finger, H. Strobel;
Ger. Offen. DE **19,** 774, 026; *Chem. Abstr.,* **130,** 267427c (1999).

40. Carbau, Romuald; Mowhray Clholes Erie; Perros, Manou Ssos; Shipple Paul Anthens, Wood, Anthony;
PCT Int. Appl. WO **02** 04,424 (Cl. C07D231 /12); *Chem. Abstr.,* **136,** 118445d (2002).

41. Ji Yang et al ;
J. Med. Chem. **47**, 1547-1552, (2004).

42. Ruoxi Lan, Qion Liu, Pusheng Fan et al ;
J. Med. Chem. **42,** 769-776, (1999).

43. Akihiko Tanitame, Yoshihiro Oyamada, Keiko Ofuji et al;
J. Med. Chem. **47**, 3693-3696, (2004) .

44. Gregory R. Bebernitz, Greg Argentieri, Beverly Battle et al ;
J. Med. Chem. **44,** 2601-2611, (2001).

45. Franco chimenti, Adriana Bolasco et al ;
J. Med. Chem. **47**, 2071-2074, (2004).

46. Abdel-rahman farghaly and hussein el-kashef et al.;
Monatshefte fur Chemie **136**, 217–227 (2005).

47. Pierluigi caboni, robert e. Sammelson, and john e. Casida;
J. Agric. Food chem. **51,** 7055-7061(2003).

48. W.Craig Lindsley, D.David Wisnoski, H.William Leister, A.Julie et al.;
J. Med. Chem. **47,** 5825-5828 (2004).

49. L.Adrian Gill, Martyn frederickson, Anne Cleasby and J.Steven Woodhead et al.;
J. Med. Chem. **48,** 414-426 (2005).

50. Jeffrey roppe, D.Nicholas Smith, Dehua huang, Lida tehrani and bowei wang et al.;
J. Med. Chem., **47,** 4645-4648(2004).

51. Bantwal Shivarama Holla , Manjathuru Mahalinga, Mari Sitambaram Karthikeyan, Padiyath Mohamed Akberali and Nalilu Sucheta Shetty;
Bioorg. and Med. Chem., 14(6), March 2040-2047 (2006)

52. U.Antoniana Krettli, O.Isabela Freitas, P.P.Rodrigo Soares et. al.;
Bioorg. and Med. Chem. Letters, **16(3),** 649-653 (2006).

53. Paolo Pevarello Daniele Fancelli, Anna Vulpetti, Raffaella Amici et. al.;
Bioorg. and Med. Chem. Letters, **16(4),** 1084-1090 (2006).

54. J. Elguero;
In Comprehensive Heterocyclic Chemistry, eds., A. R. Katritzky and C. W. res., **Vol 5,** 168 (1984).

55. R. S. Theobald;
Rodd's Chemistry of Carbon Compounds, Ed. M. F. Ansell, **Vol. IV**, Part C, Ch. 16 2nd Edition, (Elsenier Science Publishers B. V., Amsterdam) 59 (1998).

56. V. Gohanmukkala, A. Subbaraju, R. Naykula and D. Parmeswara;
Indian J. Heterocyclic Chem., **4**, 87-92 (1994).

57. Vimesh M. Patel and Kishor R. Desai;
ARKIVOC (2004) (i) 123-139.

58. M. Hassaneen Hamdi, A. E. Hamad, A. H. M. Hiyam;
Salter Lett., **8(5),** 27582 (1989); *Chem. Abstr.,* **111,** 57611 (1989).

59. M. A. El. Hashsh, M. El-Kady, M. A. Saiyed, A. A. Elsawy;
Egypt. J. Chem., **27(6)**, 715-21 (1985); *Chem. Abstr.*, **105**, 20868u (1986).

60. A. K. Padya, K. Jaggi, V. Lakshminarayana, C. S. Pande;
J. Indian Chem. Soc., **75(2),** 104-105 (1998).

61. A. M. Fahmy, M. Hassan, A. A. Khalf, R. A. Ahmed;
Rev. Roum. Chim., **33(7),** 755-61 (1988); *Chem. Abstr.,* **111,** 77898 (1989).

62. G. Gyassi, K. Bourin, M. Lamiri, M. Soufiaoui;
New Journal of Chemistry, **22(12),** 1545-1548 (1998).

63. S. Paul, R. Gupta;
Indian J. Chem., **37B,** 1279-1282 (1998).

64. A. Dandia, H. Taneja, C. S. Sharma;
Indian J. Heterocycl. Chem., (1999); *Chem. Abstr.,* **132,** 265161d (2000).

65. A. K. Reda, A. A. Khalaf, M. T. Zimaltu, A. M. Khalil, A. M. Kaddah;
J. Indian Chem. Soc., **68,** 47-51 (1991).

66. B. Roman;

Pharmazie, **45,** 214 (1990).

67. Z. Brozozowsk, E. Pormarnacka;

Acta. Pol. Pharm., **37(4),** 1378-80 (1980); *Chem. Abstr.,* **25,** 80807 (1981).

68. Archana Shrivastava V. K.; Chandra Ramesh, Kumar Ashok;

Indian J. Chem., **41B,** 2371-75 (2002); *Chem. Abstr.,* **138,** 271582 (2003).

69. H. G. Garg and P. P. Singh;

J. Chem. Soc., **2,** 1141 (1936).

70. Ashok Kumar, R. S. Verma and B. P. Jagu;

J. Ind. Chem. Soc., **67,** 120 (1990).

71. W. I. Ronald, A. Adriano;

Chem. Abstr., **126**, 181346f (1997).

72. H. M. Mokhtar, H. M. Faidallah;

Pharmazie, **42,** 482 (1987).

73. Delay Francois (Fermenich S. A.) Patent Schrift (Switz);

Chem. Abstr., **117,** 90276f (1992).

74. G.Aysel, D.Seref , C.Gultaze , E.Kevser , V.Kamil;

Eur. J. Med. Chem., **35,** 359-64 (2000).

75. P. Desaea; A. Nunrich; M. Carderny and G. Devaux;

Eur. J. Med. Chem., **25,** 285 (1990).

76. Kalluraya Balakrishna, R.Chimabalkar , G.Rai , R.Gururaja , S.Shenoy ;

J. Indian Coun. Chemi., **18(2),** 39-43 (2001); *Chem. Abstr.,* **138,** 238061 (2003).

77. Y. Hiroyuti, O. Mocoto, et al.;

Eur. Pat. Appl. Ep 295695 (Cl. C07D 401/6) (1988); *Chem. Abstr.,* **111,** 23510 (1989).

78. K. Zalgislaw, and A. Seffan ;

Acta. Pol. Pharm., **36(6)**, 645 (1979); *Chem. Abstr.*, **93**, 204525e (1980).

79. S.S. Nayal and C.P. Singh;

Asian J. Chem. **11,** 1, 207-212 (1999).

80. K. Wellinga, H. H. Eussen Jacobus;

Eur. Pat. Ep. **269** 141 (Cl C07D 231/06) (1988); *Chem. Abstr.,* **110,** 8204 (1989).

81. K. Trena and Zolzislaw;

Acta. Pol. Pharm., **36 (3),** 227 (1979); *Chem. Abstr.,* **93,** 4650r (1980).

82. D. Bhaskar Reddy, T. Senshuma, B. Seehaiha and M.V. Ramma Reddy;

Indian J. Chem., **30(B)**, 46 (1991).

83. M. K. Shivananda, P. M. Akberali, B. Holla, Shivarama, M. Shenoy, Shalini;
Indian J. Chem., **39B(6),** 440-447 (Eng.); *Chem. Abstr.,* **134,** 86195n (2000).

84. E. Palaska, M. Aytemir, I. T. Uzboy, D. Erol;
Eur. J. Med. Chem., **36(6),** 539-543 (Eng), 2001; *Chem. Abstr.,* **136,** 18374v (2002).

85. F. Manna, F. Chiments, A. Belasco, Cenicola M. L., D'Amico et al.;
Chem. Abstr., **118,** 80902p (1993).

86. S. S. Sonarc;
Asian J. Chem., **10(3),** 591-593 (1998); *Chem. Abstr.,* **129,** 633, 54317j (1998).

87. V. V. Fernandes et al;
J. Indian Chem. Soc., **74(3),** 238 (1997) (Eng.).

88. R. H. Udupi, A. R. Bhat, K. Kumar;
Indian J. Hete. Chem., **8(2),** 143-146 (1998);

89. N. Richard, M. Megan et al.;
J. Med. Chem., **36(1),** 134-139 (1993); *Chem. Abstr.,* **118,** 191847u (1993).

90. F. Rainer, E. Christoph;
Ger. Offen. DE, **4,** 336, 307 (Cl. C07D 231/16) (1995); *Chem. Abstr.,* **123,**256703u(1995).

91. Tsuboi-Shinichiwada, Katshaki et. al.;
Eur. Pat. Appl. EP, 537-580 (Cl. C07D 401/64) (1993); *JP Appl.* 91/297; 772 (1991); *Chem. Abstr.,* **119,** 139220r (1993).

92. Tuntawy, Atif, E. Fatema, A. M. Abdela;
Chim Pharm. J., **47(1),** 37-45 (1995); *Chem. Abstr.,* **123,** 228016d (1995).

93. Almstead Ji - In Kim, D. R.Jones;
PCT Int. Appl. WO **02** 89, 799 (Cl. A61K31/4439) (2002); *Chem. Abstr.,* **137,** 370086j (2002).

94. G. N. Mishrika, N. Assad, F. M. Fawzy;
Pharmazie, **53(8),** 543-547 (1998); *Chem. Abstr.,* **129,** 260380 (1998)

95. Maurer Fritz, Fuchs Rainer, Erdelen Chritoph, A.Turberg;
PCT Int. Appl. WO 03 **59,** 887 (Cl. C07 D231/28) (2003); *Chem. Abstr.,* **139,** 117441z (2003).

96. N.Gokhan , A.Yesilada , G.Ucar , K.Erol , A. A.Bilgin;
Arch Pharm. (Weinheim), **336(8)**, 362-71 (2003).

97. J.Matysiak , A.Niewiadomy ;
Bioorg. Med. Chem., **11(10),** 2285-91 (2003).

98. Z.Tabarelli , M.A.Rubin , D.B.Berlese , P.D.Sauzem , T.P.Missio , M.V.Teixeira;
Braz. J. Med. Biol. Res. **37(10),** 1531-40 (2004).

99. Tae-Sook Jeong, Kyung Soon Kim, Ju-Ryoung Kim, Kyung-Hyun Cho, Sangku Lee and Woo Song Lee;
Bioorg. Med. Chem. letters **14(11),** 2719-2723 (2004).

100. F. Chimenti, B. Bizzarri, F. Manna, A. Bolasco, D. Secci, P. Chimenti, A. Granese, D. Rivanera, D. Lilli, M.M. Scaltrito and M.I. Brenciaglia;
Bioorg. Med. Chem. letters **13(3),** 603-607 (2005).

101. Mohammad Abid and Amir Azam;
Bioorg. Med. Chem. **13(6),** 2213-2220 (2005).

108. Abd El-Galil E. Amr, Nehad A. Abdel-Latif and Mohamed M. Abdalla;
Bioorg. Med. Chem. **14(2),** 373-384 (2006).

109. Amir Azam, Asha Budakoti and Mohammad Abid;
E. J. Med. Chem., **41(1)**, 63-70 (2006).

110. Y. Rajendra Prasad, A. Lakshmana Rao, L. Prasoona, K. Murali and P. Ravi Kumar;
Bioorg. Med. Chem. letters **15(22),** 5030-5034 (2005).

102. S. D. Sorthiya, V. B. Patel, A. R. Parikh;
Indian J. Chem. Soc., **24,** 238 (1997).

103. Oza Haresh, Joshi Dharti, Parekh Hansa;
J. Inst. Chem. (India) (1998); *Chem. Abstr.*,**130**; 139682 (1999).

104. Akhil Bhatt, H. H. Parekh and A. R. Parikh;
Heterocyclic Commun., **4(4),** 361-66, (Eng.); *Chem. Abstr.,* **130,** 25006x (1999).

105. Tejas A. Upadhyay, Jawalant A. Shastri & H. H. Parekh;
Orient. J. Chem., **18(1)**, 175-76, (2002).

106. Sohit Rajvaidya, Jaladhi Vasavada & H. H. Parekh;
Ind. J. Chem., **42 B**, 906-908, (2004).

107. A. V. Dobaria, J. R. Patel & H. H. Parekh;
Ind. J. Chem., **42 B**, 2019, (2003).

111. D. L.Rector, S. D.Folz, R. D.Conklin, L. H.Nowakowski and G. Kaugars;
J. Med. Chem., **24,** 532-538 (1981).

112. R. Shridhar, G. Sivaprasad and P.T. Parumal;
J. Heterocyclic. Chem., **41,** 405-407 (2004).

113. Y. S. Sadanandam, M. M. Shetty, P. V. Diwan;
J. Med. Chem., **27,** 87-92 (1992).

114. Biginelli;
Gazz Chim. Ital. **23,** 360 (1893); Atti Accad. Licel, 3 (5), 195 (1894).

115. Hussain Ali Saleiman;
Indian J. Heterocycl. Chemistry, **11**, pp, 102 (2001).

116. V. Alagarsay, U. S. Pathak, S. Meena, K. V. Rameshu, R. Revathi, S. Amuthalakshmi, K. Thirumurugan, V. Rajasolomon;
Indian J. Heterocycl. Chem., **12,** 335-338 (2003).

117. C. C. Heidelberger, N. C. Chaudhari, P. Dannberg, D. Mooren, L. Griesbach, R. Duchinsky, R. T. Schnitzer, *E. Pleven; Scheiner* (1957), *Nature,* **179**, 663.

118. F. French;
Proc. Am. Ass. Cancer Res. **3,** 319 (1962).

119. W. Hepworth, T. W. Thompson;
Chem. Abstr., **69,** 7724 (1968).

120. G. E. Hardtmann;
U.S. **8,** 663, 698 (Cl. 424-251; 1972). Appl. 779, 200; *Chem. Abstr.,* **77,** (1972).

121. N. Tokutake;
Brit. Pat 146836B, *Chem. Abstr.,* **87,** 102370 (1977).

122. D. S. Maheson, M. S. Bleenbaum. R. A. Bechtold, R. J. Willsek.,
J. Org. Chem., **43,** 950 (1978).

123. M. Akhtar, Shamin, M. Seth, A. Baduri;
(Div. Med. Chem. Centre Drug) Res. Ints. Lucknow. India; Chem. Abstr., **108,** 15408b (1988).

124. J. A. Martin, D. J. Bushnell, Duncan;
J. Med. Chem., **33,** 2137 (1990).

125. K. A. Watanabe, K. Hurado, J. Zeidler;
J. Med. Chem., **33,** 2145 (1990).

126. V. J. Ram, N. Haque, P. Y. Guru;
Eur J. Med. Chem., **27,** 851 (1992).

127. Liu, Xungyong, Xu, Lijiun, Shandong;
Yike Daxue Xuebuo, **31(2),** 176-9 (1993).

128. M. T. Omer, H. H. Fahmy, H. S. Mohamad;
Egypt J. Pharm Sci, **37(1-6),** 609-620 (1996).

129. W. P. John, M. M. Christopher, R. R. Anthony, C. M. Vernie;
PCT Int. Appl WO, **99,** 14, 216 (Cl. CO7D 403/10) 1996; *Chem. Abstr.,* **130,** 252370e (1999).

130. Nagarathnam, Dhanapalam,; C.Wong Wai ,Maio Shou Wu,
PCT Int. Appl. WO **97,** 17, 969 (Cl. A61K 31/505); *Chem. Abstr.,* **127,** 65783t (1997).

131. M. A. Patane, M. G. Bock, H. G. Selnick;
PCT Int. Appl. WO **98,** 57, 641, (Cl. A61K 51/445); 1998, *Chem. Abst.,* **130,** 81519x (1999).

132. K. Nicholas, M. Premji, T. Stephen;
PCT Int. Appl. WO **98,** 54, 180 (Cl. CO7D 417/06) 1998; *Chem. Abstr.,* **130,** 38394 (1999).

133. Baradi P. G. et. al.;
II Famaco, (1996), **51,** 297-300.

134. L. V. Azaryan, S. A. Avetisyan, A. A. Chachoyan, N. S. Buyukyan;
Khim. Farm. Zh., **31(6),** 8-10 (1997); *Chem. Abstr.,* **127,** 262648d (1997).

135. V. P. Krivongov, G. A. Tolstiko, Ju. I. Murinov, F. A. Zarudil;
Khim. Furm. Ch, **31(6),** 23-27 (1997); *Chem. Abstr.,* **127,** 262649e (1997).

136. C. D. Timothy, M. Healtherl, J. Juanc, J. P. Poweys;
PCT Int. Appl. WO **99,** 41, 253 (Cl. CO7D 403/04); *Chem. Abstr.,* **131,** 10013 (1999).

137. Balis F. M. et. al.;
Blood, (1998), **92(10);** 3569-77.

138. A. Koties, H. Wonpyo, J. E. Semple;
US U.S., **5,** 602, 077 (Cl. 504-243, CO7D 239/553); *Chem. Abstr.,* **126,** 199577s (1997).

139. K. Mogilaiah and S. Baburao;
Indian J. Chem., **37(B),** 139 (1998).

140. A. Mona Mohran, El-Sherbeny, A. Magda, El-Obaid, M. A. Abdul-Rahman, Badria Farid;
J. Pharm. Sci., **12(1),** 39-44 (1998); *Chem. Abstr.,* **129,** 58397w (1998).

141. M. A. Bruce, G. S. Poindercter, G. Johnson;
US U.S., **5,** 889, 016 (Cl. 514-274 A 61K 31/505) 1999; *Chem. Abstr.,* **130,** 237586m (1999).

142. Angelina Quintero et. al.;
J. Pharm Pharmaceut Sci., **2(3);** 108-12, (1999).

143. M. M. Barbuliene, E. Udrenaite, P. Gaidelis, V. P. Vainila;
Polish J. Chem., **76(4),** 557-63 (2002); *Chem. Abstr.,* **137,** 154892b (2002).

144. A. M.El-Agrody, M. S.Abd Latif, N. AEl-Hady, A. H. Fakery, A. H. Bedair;
Molecules **6(6)**, 519-27 (2001); *Chem. Abstr.*, **136 (12)**, 183779e (2002).

145. F. F.Patricia, U. I.Amalia, J. LGuillen, M. Eugenia;
Eur. J. Med. Chem., **38,** 289-96 (2003).

146. Dumas Jacques, C. E.Icluender Harald, Zhang Chengzhi;
PCT Int. Appl. WO **03** 40, 141 (Cl. CO7D 413/14) (2003); *Chem. Abstr.,* **138,** 860 (2003).

147. Tsann-Long Su, et. al.
Bioorg & Med. Chem., **11(1),** p. 145-47 Jun (2003).

148. Richard J. Perner et. al.;
Bioorg & Med. Chem., Lett., **15(11),** (2005).

149. Sharad Verma et. al.;
Bioorg & Med. Chem. Letter., **15(8),** p. 1973-77 April, (2005).

150. Vinay Lathey & A. K. Madan,
Bioorg & Med. Chem., **13(5),** p. 1599-04 March, (2005).

151. Aleem Gangjee, Hitesh Kumar, D. Jain & Roy L. K. Kishuk,
Bioorg & Med. Chem. Lett, **15(9),** 2225-30 May (2005).

152. Antonello. Mai. et. al;
Bioorg & Med. Chem., **13(6),** p. 2005-2077 Mar (2005).

153. Maria T. Cocco, Cenzo Congiu, Valentina Lilliu and Valentina Onnis;
Bioorg. and Med. Chem., **14(2),** 366-372, Jan. (2006).

154. Rudolf Waelchi, Birgit Bollbuck, Christian Bruhl, Jorg Eder, Roland Feifel, Rene Hersperger, Philipp Janser, Achim Shlapbah;
Bioorg and Med. Chem. Lett., **16(1)**, 108-112, Jan (2006).

155. Naveen Chandra, Sumita Pandey, Ramesh, S. N. Suryawanshi, Suman Gupta;
European Journal of Med. Chem., **41**, 779-785 (2006).

156. Vogel's Text book of practical organic chemistry;
5th Addition, methods No. 6.**97,** Page No. 964.

157. M. Saeda, M. Abdel-Metgid and I. M. El-Deen;
Indian J. of Heterocycl. Chem., **3,** 81-86 (1993).

158. J.Rosallen Anderson, S.Anderi Batsanov, Natalia Belskaia, W.Paul Groundwoqer, Andrey Zaytsev;
Tetrahedron Letters., **45(5)**, 943-946, Jan. 2004.

159. Strache;
Ber. **21,** 2361 (1888).

160. M. S. Murray;
Chemical Review **26,** 297-338 (1940).

161. Ergenc Nedime, Uinsoy Nuray, Capangultate Soruis, Aulten O Tuk, Kiraz Mnammer;
Arch. Pharm., **329(8-9)**, 427-430 (1996); *Chem. Abstr.*, **126(1)**, 8031b (1997).

162. A.Adnan Bekhil, T. V.Heshan Fahwy, Azzaim Baraka et al.;
Eur. J. Med Chem., **38,** 27-56 (2003).

163. R. P. Pawar, N. M. Anduskary, V. B. Vibhute;
J. Indian Chem. Soc., **76(5)**, 271-272 (1999); *Chem. Abstr.*, **131**,677, 271829y(1999).

164. T. Omar Mahmoud;
Egypt J. Pharm. Sci., **38**, 271-280 (1997): *Chem. Abstr.*, **131**,645, 257474x (1999).

165. Pascal Rathelst, Nadine Azos, Hussain El-Kashef, Forence Delwasi;
Eur. J. Med Chem., **57,** 671-679 (2002).

166. Wang Yangang, Ye. Wenfa, Yang Jun., Lou Aihong, Wurhan Daxue Xuebao, Ziran Kexueban;
Chem. Abstr., **125(13)**, 167488b (1996).

167. Das Arima Lien, J. Eric, TRousdale, D. Melvin;
Chem. Abstr., **128(18)**, 217259n (1998).

168. Cascaval Alexandru, Stocia, Gheorghe-Zaharia, Berdan Ioan;
Rom. Ro., **106**, 403 (Cl.C07D 231/04) (1993); *Chem. Abstr.*, **129**, 2, 491, 16120g (1998).

169. B.Shivarama Holla, B. Sooryanarayana Rao, K. Shridhara and P.M. Akberali;
IL Farmaco, **55, 5** 338-344,(2000).

170. Jerpan Krungkrai, Andred Scozzafava,Sutarnthip, Reungprapavnt, Sudaratana R. Krunkrai, Roonglawan Rattaanajk Sumalee, Kamchonwong Paisan and Claudi T Supuran;
Bioorg. Med. Chem. **13,** 483-489 (2005).

171. A.Popesal, A.Simion, A. Scozzafava, F.Briganti and C. T. Supuran;
J. Enz. Inhib., **14(6) ,**407-423 (1999).

172. Ergenc Nedime, Uinsoy Nuray, Capangultate Soruis, Aulten O Tuk, Kiraz Mnammer;
Arch. Pharm., **329(8-9)**, 427-430 (1996); *Chem. Abstr.*, **126(1)**, 8031b (1997).

173. H. Afaf, El-Musry, H. H. Fahmay and S. H. Ali Abdewahed;
Molecules, **5,** 1429-1438 (2000).

174. Wang Yangang, Ye. Wenfa, Yang Jun., Lou Aihong, Wurhan Daxue Xuebao, Ziran Kexueban;
Chem. Abstr., **125(13)**, 167488b (1996).

175. Nadine Azas, Pascal Rathelot, Serge Djekou, Florence Delmas, A. Gellis, Carole Di Gsorgic, Patrice Vanelle andPierre timon-David;
IL Farmaco, **58,** 1263-1270 (2000).

176. Jayendra Patole, Uday sandbhor, Subhash Padhye, dileep N. Deobagkar, Christopher E. Anson and Annie Powell;
Bioorg. Med. Chem. Lett., (2003).

177. J.M. Monti, H. Jantos, A.Pnzoni and D.Monti;
European Neuropsycho Pharmacology, **6,** 74 (1996).

178. S. Guniz Kucukguzel, Ilkay Kucukguzel, sevim Rollas, Gulten Otuk-Sanis, Osman Ozdemir, Ibrahim Bayrak, Tuncay Altug and James P stables;
IL Farmaco, **59,** 893-901 (2004).

179. Huseyin Unver , Mustafa Yildiz , Basaran Dulger , Ozgen, Engin Kendi and Tahsin Nuri Durlu;
J. Molecular structure, **737,** 159-164 (2005).

180. Neslihan Demirbas and Reyhan Ugurluogul;
Turk. J. Chem., **28, 679-690** (2004).

181. R.S. Varma;
J. Indian Chem. Soc., **81, 8** 627-638 (2004).

182. Christos A. Kontogiorgis and Dimitra J. Hadjipavlou-Litina;

183. Ilkay Kucukguzel, S. Guniz Kucukguzel, sevim Rollas, Gulten Otuk-Sanis, Osman Ozdemir, Ibrahim Bayrak , Tuncay Altug and James P stables;
IL Farmaco, **59,** 893-901 (2004).

184. Perumal Panneerselvam, Rajasree R. Nair, Gundaparthi Vijyalakshmi, E.K. Ambaram, Harihara Subramaniam and Seshaiah Krishnam Srithar;
Eur. J. Med Chem., **40,** 225-229 (2005).

185. Hojatollah Matioubi , Abbas Shafiee , Nader Saemian , Gholamhossein Shrivani, Fariba Johari Daha;
Applied Radiation & Isotopes., **60,5,** 665-668 (2004).

186. Sham M. Sondhi , Nirupma Singh , Ashok Kumar , Olivier Lozach and Laurent Meijer;
*Bioorg. Med. Chem.***,14,** 3758-3765 (2006).

187. Zhanyong Guo, Rong Chen, Ronge Xing, Song Liu, Huahua Yu, Pibo Wang, Cuiping Li and Pengcheng Li;
*Carbohydrate Research.***, 341,** 351-354 (2006).

188. Alladdin Cukurovali , Ibrahim Yilmaz , Kavit Kazaz;
Eur. J. Med Chem., **41,** 201-207 (2006).

189. Jayendra Patole, Dipti Shingnapurkar, subhash Padhye and Colin Ratledge;
Bioorg. Med. Chem. Lett., **16,** 1514-1517 (2006).

190. Dharmarajan Shriram, Perumal Yogeeswari, Nega Shrisha Myneedu and Vivek Saraswat;
Bioorg. Med. Chem. Lett., **16,** 2127-2129 (2006).

191. A. W. Hoffman;
Ber., **2 1**, 2332 (1880).

192. A. Ladenburg;
Ibid., **27**, 2952 (1894).

193. Zednikova Gabriela, Nalepa Karela;
Acta Univ. Palacki Olamuc., Fac. Rerum Nat. Chem., 1998; *Chem. Abstr.,* **131**, 116188v (1999).

194. C. Granachar and G. Gulbas;
Helv. Chem. Acta., **10**, 818-26 (1927); *Chem. Abstr.,* **22**, 781 (1928).

195. H. A. Allimony, Sadd H. A. and F. A. A. el-Mariah;
Indian J. Chem., **38(B),** 445 (1999).

196. A. Saxena, N. C. Desai, Kesha K. Awasthi;
Indian J. Chem., **40(B)**, 201 (2001).

197. Feng Jun-Cai, Meng Quing-Hug, Liu Yang, Dai-Li;
Org. Prep. Proceed Int., (1997); *Chem. Abstr.,* **128**, 61455k (1998).

198. Hisato Takeuchi, Satosh; Hagiwara & Shoji Eguchi;
Tetrahedron, **45(20),** 6375-6386 (1989).

199. Laszlo Varga, Tamas Nagy, Gyorgy Dorman and Ferenc Darvas;
Tetrahedron, **59(5)**, 655-662 (2003).

200. A. Sudhir and P. C. Dandiya;
Proc. Dec. Conf. Ind. Pharmacal. Soc. Abs. No. **88** (1977).

201. S. M. Sethna and R. C. Shah;
J. Indian Chem. Sci., 1459 (1993).

202. Sanjay Swaroop, V. K. Saxena and S.R. Chowdhary;
Indian J. Pharma. Soc., **51(4),** 124-27 (1989).

203. M. Verma, A. K. Chaturvedi, A. Chaudhari, S. S. Parmar;
J. Phar. Sci., **63,** 1740-44 (1974); *Chem. Abstr.,* **82,** 51358y (1975).

204. K. K. Kataryna, E. Szymanska, M. Motyl, W. Holzer, A. Bialecka, Kasprowicze;
Pharmazie, **53(10),** 680-684 (1998); *Chem. Abstr.,* **130,** 3606f (1999).

205. A. J. Srivastava, Sanjay Swaroop, V. K. Saxena and P. Srivastava;
Indian J. Pharma. Sci., **51(6),** 23, (1989).

206. P. K. Naithani, V. K. Srivastava, J. P. Barthwal, A. K. Saxena, T. K. Gupta and K. Shanker;
Indian J. Chem., **28B,** 990-92 (1989).

207. K. A. Johnnes, K. Kauko, O. A. Seppo, Sulevi Lennart;
Eur. Pat. Appl. EP **58** 047; *Chem. Abstr.,* **98,** 16692m (1983).

208. Thomas I. Kalman;
PCT Int. Appl. WO **94** 21,658 (1994); *Chem. Abstr.,* **122,** 315045k (1995).

209. R. R. Grenshaw and Luke George M.;
Can. CA., **1,** 130, 306; *Chem. Abstr.,* **98,** 16649p (1983).

210. Desalns S Jane, Shaw Anthony W.;
PCT Int. Appl. WO **99,** 8,096 (Cl. C07 P401/02) (1999); *Chem. Abstr.,* **131,** 167431z (1999).

211. Arnould Jean-Cldude, Francis Thomas Boyle;
PCT Int. Appl. WO **98,** 32,741 (1998); *Chem. Abstr.,* **129,** 16156f (1998).

212. K. Kawasaki, H. Kobayashi, S. Ehara, Hideaki Sato;
PCT Int. Appl. WO, **98** 32, 740 (Cl. C07D 223/60) (1998); *JP. Appl.* 97, 110, 114 (1997); *Chem. Abstr.,* **129,** 148945h (1998).

213. K. C. Mathur and R. Sahay;
J. Indian Chem. Soc., **67,** 856 (1990).

214. Chang Lind di;
PCT Int. Appl. WO, **98** 22, 208 (1998); *Chem. Abstr.,* **129,** 41134x, (1998).

215. Hussieny Hamed Moharram, R. Samiya El-Amin and Ahmed El-Dawany;
J. Serb. Chem. Soc., **54(7)**, 335-42 (1989); *Chem. Abstr.,* **114**, 101822x (1991).

216. M. B. Gravestock and J. F. Ryley;
"Antifungal Chemotherapy in annual reports in medicinal chemistry." **19,** 127 (1984).

217. V. K. Pandey and (Ms.) Meenal Tandon;
Ind. J. Chem., **40B,** 527-29 (2001).

218. C. R. Sharma and D. R. Shridhar;
Indian Pat., *IN* 154-314 (1984); *Chem. Abstr.,* **105,** 133738 (1986).

219. E. Bousquet, G. Romeo, N.A. Santagati, T. Lancetta, A. Caruso, V. Leone, and A. Felice;
Farmaco., **44(9),** 851-63 (1989); *Chem. Abstr.,* **112,** 191378t (1990).

220. R. Agarwal, C. Chaudhary and V. S. Misra;
Indian J. Chem., **22(B)**, 308 (1983); *Chem. Abstr.,* **99**, 881280 (1983).

221. J. M. Altenburger, L. Gilbert;
Chem. Abstr., **131,** 76653y (1999).

222. Vedu Akyoshi, Myazawa Yasuyuki;
Jpn. Kokai Tokkyo Koho, JP **7** 206, 829 (1995); *Chem. Abstr.,* **123,** 283031 (1995).

223. Kolhe Vishnu, Dhingra Vinod;
Ind. J. Heterocycl. Chem., **4(1),** 69-70 (1994); *Chem. Abstr.,* **122,** 105757l (1995).

224. T. Kitazaki, A. Tasaka, H. Hosono, Y. Matsushita, K. Itoh;
Chemical and Pharmaceutical Bulletin, **47(3)**, 351-359 (1999).

225. Ozaki Satoshi, Kacoamoto Hiroshi Ito Yoshiki, Hirano Kaori, Hayashi Kyoko;
PCT Int. Appl. WO **98,** 54, 168 (Cl. CO7D401/04) (1998); *Chem. Abstr.,* **130(5),** 52418q, (1999).

226. Lacroix Guy, Peignier Raymond, Pepin Regis, Bascou Jeanphilippe, Perer Joseph;
US, U.S. B, 00 2, 016 (1999); *Chem. Abstr*., **132,** 356998c (2000).

227. Rama Sharma and Biplab De;
Ind. J. Heterocycl. Chem., **9,** 185-188. (2000).

228. K. K. Awashthi; A. K. Saxena;
Indian J. Chem., **40B,** 207 (2001).

229. Imam Hidayat and Christopher Preston;
Pestiade Biochemistry and Physiology, **71(3),** 190-195, Nov. (2001).

230. Keun-Jin Oh, Eun-Joung Park, Moon-Yoring Yoon, Tae-Ryong Han, and Jung Do Choi;
Biochemical and Biophysical Research Communications., **282(5)**, 1237-1243, April-(2001).

231. Stefama Lauter, Hans Gunther, Gerd Wagnewr;
J. Medicinal Chem., **45,** 4695-4705 (2002).

232. Declera Erickl, Van Aerschot Arthur, Herdeciln Piet;
PCT Int. Appl. WO **02** 68, 395 (Cl. C07D 235/84) (2002); *Chem. Abstr.,* **137,** 201308c (2002).

233. Ding Ming Wu, Zhifeng Ziu, Ying Yong, Hy axye;
Chem. Abstr., **136,** 5497 (2002).

234. M. L.Irene, P.Christophe, A. Arthur Van, Myrian Witwrouas, Zeger Debyser;
J. Med. Chem., **46(8),** 1546 (2003).

235. Zhong Jin;
Nat. Prod. Rep. (2003), **20,** 584-605.

236. M. R.Jean, Carolin Sabourin, Nidia Alvorez, R. P.Sylvie, L. B.Guillaume , L.P.Patrice;
Eur. J. Med. Chem., **38,** 711-718 (2003).

237. Preeti Kagthara, Niraj Shah, Rajeev Doshi & Hansa Parekh;
Heterocyclic Communication, **4(6),** (1998).

238. A. H. Bhatt, K. A. Parikh and A. R. Parikh;
Ind. J. Chem., **38(5)B,** 628-631 (1999).

239. R. C. Khunt, N. J. Datta and A. R. Parikh;
Ind. J. of Pharm. Sci., **170,** (2002).

241. Hasmukh Knjariya, Devendra Verma and Hansa Parekh;
Orient. J. of Chem., **18(3),** 583, (2002).

242. Satyen P. Patel, Ashutosh M. Joshi, Ketan V. Hirpara and H. H. Parekh;
Orient J. of Chem., **19(2),** 435, (2003)

243. H.Joshi, P. Upadyay, D.Karia, A. J. Baxi;
Eur. J. Med. Chem., **38(9),** 837-840, (2003).

244. N.Aleksey Vasiliev, F. Antonio Lopez, D. Julio Fernandez and J. Anibal Mocchi;
Molecules, **9,** 535-540, (2004).

245. C. Alister and M. Kogan;
Grop Protectien, **24(4),** 375-379, April (2005).

246. E. Jayachandran, H. S. Basavaraj, G. M. Sreenivasa, L. V. G. Nargund and D. Sreenivasa Rao;
*Indian J. Heterocyclic Chem.,***15(1)***,* 69-70, (2005).

247. S.Tan ,R Evans ., B.Singh ;
Amino Acids, **30(2),** 195-204 (2006).

248. W. Russel Bowman, Colin F. Bridge, Philip Brookes, Martin O. Cloonan and David C. Leach;
J. Chem. Soc., Perkin Trans., **1**, 58-68 (2002).

249. Rajul Jain, Frank Roschangar, Marco A. Ciufolini;
Tetrahedron Lett., **36(9)**, 3307-3310 (1995).

250. K. Folkers, S. A. Harris;
J. Am. Chem. Soc., **61**, 1245 (1939).

251. Hu Zhiyong, Wang Huicai;
Chem. Abstr., **119**, 72465d (1993).

252. U. Toru, T. Susumu, E. Masayuki and S. M. Saharu;
Eur. Pat. Appl. EP. 4 **88**, 220 (Cl. C07D 413/04) (1992); *Chem. Abstr.,* **118**, 80944d (1993).

253. R. W. Hartann, N. Reichert and S. Gozhring;
Eur. J. Med. Chem., **29**(11), 807-17 (1994); *Chem. Abstr.,* **122**, 239500n (1995).

254. K. Jonhannes, F. Rainer, J. R. Jansen and S. Nichael;
Ger. Offen. DE 4, **309**, 552 (Cl. C07/D 213/85); *Chem. Abstr.,* **122,** 9877m (1995).

255. D. D. Erol, N. Yulung and A. Turk;
Eur. J. Med. Chem., **29(11),** 893-7 (1994); *Chem. Abstr.,* 122, 13650a (1995).

256. P. Fey, H. K Rudolf, H. Walter and K Thomas;
Eur. Pat. Appl. Ep. **62,** 3611, (Cl. C07D 401/14); *Chem. Abstr.,* 122, 55897r (1995).

257. H. Rudolf, H. Walter, D. Juergen and F. Peter;
Eur. Pat. Appl. Ep. 5 **57**, 843 (Cl. C07D 401/12); *Chem. Abstr.,* **120**, 8478d (1994).

258. H. Michael, Haesslein Jean-Iuc and H. Bertrand ;
PCT Int. Appl. WO **93** 16, 149 (Cl. C07D211/86); *Chem. Abstr.,* **120**, 106778w (1994).

259. R. Bernd, P. A. Schirwan, R. Dieter, R. Guenther;
PCT. Int. Appl. WO ***96*** 30, 342 (Cl. C07D 213/89); *Chem. Abstr.,* **126**, 7993e (1997).

260. F. Al-Omar, A. Abdul Zahar, A. El-Khair, A. Adel;
Chem. Abstr., **136**, 309834q (2002).

261. F. Peter, D. Juergem, H. Rudolf, H. Walter and K Thomas;
Eur. Pat. Appl. EP. **62** 3611 (Cl. C07D 401/14); *Chem. Abstr.,* **122,** 55897r (1995).

262. H. Posnes;
Org. Synth. **177** (1994); *Chem. Abstr.,* **123**, 167349g (1996).

263. Mukhtar Hussain Khan, Raizul Haque andNizamuddin;
Indian J. Chem., **37(B),** 1069 (1998).

264. Mukhtar Hussain Khan, Raizul Haque, Taruna Agrawal and Nizamuddin;
Indian J. Chem., **38(B),** 452-456 (1999).

265. M. K Morishita, A. Nagisa and J. Masashi;
PCT Int. Appl. WO ***99*** 43, 659 (Cl. C07D 213/72); *Chem. Abstr.,* **131,** 170353h (1999).

266. I. J. Collins, L. P. David and M. C. Richard;
PCT Int. Appl. WO 98 **55,** 480 (1998); *Chem. Abstr.,* **130,** 38376t (1999).

267. Pedneker;
PCT Int. Appl. WO **98** 30, 342 (1998); *Chem. Abstr.,* **130,** 487191 (1999).

268. E.Abd El-Galil and E. Amer;
Indian J. Heterocyclic Chem., **10,** 49 (2000).

269. Abou El-Fotooh, G. Hammam, M. A. Sharaf and N. A. Abd El-Hafeza;
Indian J. Chem., **40(B),** 213-221 (2001).

270. M. G. Nizamuddin, K. S. Manoj;
Chem. Abstr., **136,** 279375x (2002).

271. Tanaka Akira, Minagawa Masatoshi, Akahane Atsyshi;
Chem. Abstr., **139,** 22210J No. 2 (2003).

272. Xi Qi, Chang ian-Hua, Ding Yi-Xiang; Youji Huaxue, 21(10), 755-758 (Ch.) (2001);
Chem. Abstr., **136(9)**, 134840j (2002).

273. G. Darcq Michael et. al.;
PCT Int. Appl. WO **03**, 59, 356 (Cl.A61K31/542) (2003). *Chem. Abstr.*, **139(9)**, 133573z (2003).

274. Isobe Yoshiaki, Tobe masanori;
Jpn. Kokai Tokkyo Koho JP., 212, 872, (Cl. C07D405/12) (2003); *Chem. Abstr.*, **139(9)**, 133583c (2003).

275. K.N.ersesyan, G. S. Melikyan, H.Stopper;
Tsitol Genet., **38(4)**, 44-8 (2004).

276. Devdas Balekudra et. al.;
PCT Int .Appl. WO **03**, 68, 230 (Cl.A61K231/44/2) (2003); *Chem. Abstr.*, **139(13)**, 197371g (2003).

277 S.Wang, L.Cao, H.Shi, Y.Dong, J.Sun, Y.Hu;
Chemical and pharmaceutical Bulletin, **53(1),** 67-71 (2005).

278. Jason witherington, Vincent Bordas, Alessandra Gaiba, M. Phil Green, Antoinette Naylor;
Bioorg. and Med. Chem. letters, **16(8)**, 2256-2259 (2006).

279. Q. Jiang, T.Zhu, D.Mc Gee, J.Wang, D. Mc Grath, S. W.Morris;
J. Med. Chem., **49(3)**, 1006-15 (2006).

280. S. G. Krivokolysko;
Chem. Heterocycl. Compd., (N.Y.) (1999).

281. U. D. Dayochenko;
Russ. J. Org. Chem., **34(4),** 554-56 (1998); *Chem. Abstr.,* **130,** 223222c (1999).

282. Okazoe Takashi;
PCT Int. Appl. WO, **00** 06, 347; *Chem. Abstr.,* **132,** 321784y (2000).

283. M. L. Crossley, V. L. King, L. H. Northey, T. E. Scholz;
U.S. US 02 **491,** 253 (1949); *Chem. Abstr.,* **45,** 4746 (1968).

284. G. H. Sayed, R. R. Kassab;
Bull. Fac. Pharma., 1998 ; Chem. Abstr., **131,** 15727p (1999).

285. A. Sakuri and H. Midorikaw;
Bull. Chem. Soc. Japan, **40**, 1680 (1967); *Chem. Abstr*; **67**, 9021d (1968).

286. A. Samour, Y. Akhnookh and H. Jahine;
U.A.R. J. Chem., **13(4),** 421-37 (1971); *Chem. Abstr.,* **77,** 101348 (1972).

287. Amalia Ubeda, Patricia Fernandez-Ferri, Isabel Guillen, Jamal Lasri, Mohamed Akssira;
Eur. J. Med. Chem., **38**, 289-296 (2003).

288. Dao-Lin Wang & Kimiaki Imafuky;
*J. Heterocyclic Che*m., **37(NOS 5-6)**, p.1019-1032. (2000).

289. Thiele Kurt, Von Be Benburg and E.Walter .;
S. African **6,** 905, 06, 13 Feb. (1970).

290. B. John ED., Freeman and F. M.Peter .;
Ger. Often., **2,** 029, 079 (Cl. A 01 N007d) (1971); *Brist. Appl.* (1969); *Chem. Abstr.,* **74,** 99891d (1971).

291. V. Scott and Joseph;
Jap. Pat., **2,** 803, 592 (1979); *Chem. Abstr.,* **92,** 47216 (1980).

292. F.Al-Omar ,A.Abdul Zahar, A.El-Khair,A.Adel;
Chem. Abstr., **136,** 3098349, (2002).

293. N. Latif, N. Mishrky and N. S. Girgis;
Indian J. Chem., **20B,** 147-149 (1981).

294. W. Von Behenburg, J. Engel, J. Heese and K. Thiele;
Ger. Often., D.E., **3,** 337, 593 (Cl C07D 213/72) 1984; *Chem. Abstr.,* **101,** 130595n (1984).

295. L. Castedo, J. M. Quintela and R. Riguers;
Eur. J. Med. Chem. Chim. Ther., **19(6),** 555 (1984); *Chem. Abstr.,* **103,** 37337 (1985).

296. M. R. Pavia, C. P. Taylor, F. M. Hershenson and S. J. Lobbestael;
J. Med. Chem., **30,** 1210 (1987).

297. M.Hussans, H. AEman., A. A. El-maghruby;
Chem. Abstr., **127**, 638p, 190698 (1997).

298. U. Teu, K. M. Takuro, M. Shinkya, K. Seiikhi;
Jpn. Kokai Tokkyo Koho JP, **09**, 95, 489 (1997); *Chem. Abstr.*, **127**, 17699y (1997).

299. H. Yoshida, K. Omori, Y. Yasuyuki, F. Kensaku;
Jpn. Kokai Tokkyo Koh. JP, **10**, 120, 677; *Chem. Abstr.*, **129**, 16062q (1998).

300. G. S. Gadaginamath, A. S. Shyadigeri and R. R. Kavali;
Indian J. Chem., **37B**, 1137c (1998).

301. M. Bernard, W. Johan, p. Lionel, L. Didier;
J. Med. Chem., **41(17)**, 3239-3244 (1998); *Chem. Abstr.*, **129**, 202846y (1998).

302. D. G. Bhatt, J. J. Petraitis, S. R. Sherk, R. A. Copeland;
Bioorg. Med. Chem., Lett., **8(13)**, 1745-1750 (1998); *Chem. Abstr.*, **129**, 202848a(1998).

303. Guru S. Goda Ginamath, S. Ashok. Shya digeri and R. Rajesh Kavall;
Ind. J. Chem., **37(B),** 1137C (1998).

304. A. John Tucker, A. Debra, Allwine, C. Kevin, Grega et al.;
J. Med. Chem., **41,** 3727-3735 (1998).

305. M. Fedele, C. Franco, B. Adriana, B. Bruna, F. Walter, F. Amelia, G. Luigi;
Eur. J. Med. Chem., **34(3)**, 245-254 (1999); *Chem. Abstr.*, **130**, 352178s (1999).

306. E. G. Hammana Abou, El-Hafeza Nagla A. Abd, Z. Midurus Wandall, B. Naturforsch;
Chem. Sci., (2000).

307. N. A. Abdallah, E. A. Zakimagdi;
Acta Pharm (Zagreb) (1999): *Chem. Abstr.*, **132**, 137287n (2000).

308. A. El-Galil and E. Amr;
Indian J. Heterocyclic Chem., **10**, 49-54 (2000).

309. El-Nabawia El-Said Goda, F. Alexandria;
S. Pharm. Sci., (1999): *Chem. Abstr.,* **132,** 151650g (2000).

310. S. V. Roman, U. D. Pyachenko;
Chem. Abstr., **136**, 325448x (2002).

311. F. M. A. El-Taweel, M. A. Sofan;
Egyptian J. Med. Chem., **36(2)**, 539-544 (2002) (Egy); *Chem. Abstr.*, **137**, 63154w (2002).

312. U. D.Pyachenko, S. V.Roman;
National nogo Uni., 495-59-64 (Russ.); *Chem. Abstr.*, **136(21)**, p-807, 325448x (2002).

313. Abu-Shana B, Fathi A, Satyed Ahmed Z, El-Gaby;
Al-Azhar Bulletin of Sci., 1999, **10(1)**, 63-70 (Eng.); *Chem. Abstr.*, **136**, 85768f (2002).

314. J. L.Marco, M. C.Carreiras;
Mini. Rev. Med. Chem., **3(6),** 518-24, (2003).

315. Edwin B. Villhauer, John A. Brinkman, Goli B. Naderi, Beth E. Dunning, L. Bonnie;
J. Med. Chem., **45,** 2362-2365 (2002).

316. Rosentreter Ulrich, Kraemer Thomas et al.;
Ger. Otten. DE 10, 238, 113 (Cl,CO 7D213/60) (2003).

317. M. A.Moustafa, M. N.Nasr, M. MGineinah, W. A. Bayoumi;
Arch Pharm. (Weinheim), **337(3)**, 164-70, (2004).

318. H. S. Eduardo Sousa, L.Daniel Pontes, C. N. Izaura Diogenes, G. F. Luiz Lope;
Journal of Inorganic Biochemistry, 368-375, (2005).

319. Gary T. Wang, Xilu Wang, Weibo Wang, A. Lisa Hasvold, Gerry Sullivan, W.Charles;
Bioorganic & Medicinal Chemistry lett., **15(1),** 153-158, (2005).

320. Abdel-Galil E. Amr and M.Mohamed Abdulla;
Bioorganic & Medicinal Chemistry, **14(13)**, 4341-4352 (2006).

321. L. Claisen and O. Lowmann;
Chem. Ber., **21**, 1149 (1888).

322 A. Quelico;
Chem. Heterocycl. Compd. **17**, 1 (1962).

323. V. B.Tayade, V. S.Jamode;
Asian J. Chem., **9(4)**, 866-68 (1997); *Chem. Abstr.*, **128**, 88824s (1998).

324. Peng Weimin, Zhu Shizheng and Jin Guifang;
Tetrahedron, **57(27)**, 5781-5784 , July (2001).

325. L. S. Crawley and W.J. Fanshawe;
J. Heterocycl. Chem., **14**, 531 (1977).

326. Issa Yavari and Loghman Moradi;
*Tetrahedron lett.,vol.***47(10)**, 1627-1629 (2006).

327. F. John Hansen and A. Scott Strong;
J. of Heterocycl. Chem., **14**, 1289 (1977).

328. I. A. Shehata and R. A. Glannoh;
Indian J. Heterocyclic Chem., **24**, 1291 (1987).

329. M. D. Mackie, H. S. Anthony, W. J. R. Howe, S. P. John and W. S. Marry;
Brit.; *UK Pat. Appl. GB* **2**, 265, 371 (Cl. C07 D 261/06); *Chem. Abstr.*, **120**, 164153z (1994).

330. G. D. Diana and C. P. Michel;
S. African ZA, **81,** 03, 105 (1981); *Chem. Abstr.,* **98,** 1667, (1983).

331. M. Moriyusu, H. Yusui;
Gen. Offen. DE **3,** 237,149 (Cl. CO7A 261114) (1983); *Chem. Abstr.,* **99,** 88188 (1984).

332. A. K. Banerjee;
Arzneim Forsch., **44**, 863 (1994); *Chem. Abstr.*, **122**, 160522n (1995).

333. M. Tibor, P. S. Neil and S. P. Henry, Gount;
PCT Int. Appl. Wo 9414, 782(Cl. C 07D 261/08); *Chem. Abstr.,* **121**, 255784t (1994).

334. Inai, Masatoshi, Tanaka, Akie, Goto, Kyoto;
Jpn Kokai Tokkyo Koho JP **07**, 215, 952 (95, 215, 952) (1995); *Chem. Abstr.,* **124**, 86995s (1996).

335. Nippon Chemiphar Co. Ltd.;
Jpn. Kokai Koho JP **58,** 46,077 (Cl. CO7A 261/14) (1983); *Chem. Abstr.,* **99,** 17574 (1984).

336. T. Taate, K. Natira and H. Fukhola;
Chem. Pharm. Buld., **35(9),** 37769 (1987); *Chem. Abstr.,* **108,** 186621e (1988).

337. D. J. David, D. B. Allon and E. A. Frederick;
Ger. Offen., **2,** 723,688 (Cl. A01N 9/28) (1977); *Chem. Abstr.,* **88,** 132015k (1978).

338. Sezer Ozkan, Debak Kudir, Anac Okay, Akar Ahmet;
Heterocycl. Commun., (1999); *Chem. Abstr.*, **131**, 5221f (1999).

339. S. Suzuki, K. Ueno and K. Mori;
Yakugaku Kenkua, **34,** 224-31 (1962); *Chem. Abstr.,* **57,** 16754 (1962).

340. B. Victor, J. Safir and R. Sidney;
Brit. 1, **178**, 604 (Cl. C07D), 21 Jan. 1970, US *Appl*. 21 Mar. (1966); 8 pp. *Chem. Abstr.,* **72,** 79017d (1970).

341. G. P. Reddy, E. Rajendra and A. K. Murthy ;
Indian J. Heterocycl. **3**, 233 (1994); *Chem. Abstr.*, **122**, 105724e (1995).

342. T. Tochiro, K. Shrji, I. Shinji, M. Hiroshi, S. Akira, V. Hiroshi;
Gen. Offen. DE **3,** 237,149 (Cl. CO7A 261114) (1983); *Chem. Abstr.,* **99,** 88188 (1984).

343. T. U. Quazi ;
Pak. J. Sci. Ind. Res., **27**, 326 (1984); *Chem. Abstr.*,**103**, 12339m (1985).

344 R. Major, B. Eisele, P. Mutler and H. Grube;
Ger. Offen. DE 3621372 (1988); *Chem. Abstr.,* **108,** 67456r (1988).

345. Vamanauchi Pharm. Co. Ltd.;
Jpn Kokai Koho JP **58,** 148, 858 (Cl. CO7D 207/333) (1982); *Chem. Abstr.,* **100,** 34538 (1984).

346. P. T. Gallagher, T. A. Hicka and G. W. Mullier;
Eur. Pat. Ep **2** 57, 882 (1988); *Chem. Abstr.,* **108,** 6499K (1988).

347. A. Ando and R. W. Stevens;
PCT Int. Appl. WO **94**, 12, 481 (Cl. C07 D 261/04); *Chem. Abstr.*, **122**, 56037x (1995).

348. W. Wells, A. Michele, H. Todd, H. Dennis;
J. (USA), US Pat. Appl. Publ. US 2002, **49**, 213, (Cl. 514-252, 05; C07D 413/02), 25 Apr. (2002); US Appl. PV 209, 6 Jun. (2000); 19 p.p. (Eng.)*; Chem. Abstr.,* **136,** 340680j (2002).

349. R. Ulrich, H. Rolf;
Chem. Abstr., **134,** 311203k (2001).

350. Qi, Chuanmin; Wang, Yangeng; Zhang, Guanxin; Feng, Shujuan;
Chem. Abstr., **137,** 370004f, (2002).

351. Wu, Chengde, Raju, Bore Gowda; Krgan, Timothy; Blok, Natalie;
Chem. Abstr., **137,** 93741e No 7 (2002).

352. Caroline Charliey, Catherin Michaux;
Eur. J. Med. Chem., **38,** 645-659 (2003).

353. Bente Frolund, R. Jeremy, Greenwood, M. Mai , Holm et. al.;
*Bioorg. & Med. Chem. vol.***13(18),** 5391-5398, (2005).

354. M. R. Barbachyn,G. J.Cleek , L. A. Dolak , S. A. Garmon, J. Morris, E. P.Seest;
J. Med. Chem. **46(2),** 284-302 (2003).

355. M. W.Salter;
J. Orofac Pain., 18(4), 318-24 (2004).

356. D. R. Mehlisch, P. J. Desjardins, S. Daniels, R. C. Hubbard;
J. Am. Dent. Assoc., 135(11), 1578-90 (2004).

357. P. M.Welsing, J. L. Severens, M. Hartman, P. L. Van Riel., R. F. Laan;
Arthritis Rheum., **51(6)**, 964-73 (2004).

358. A. V. Dobaria, J. R. Patel and H. H. Parekh;
Ind. J. Chem., Vol. **42B**, 2019-2022, Aug. (2003).

359. V. B. Patel, S. D. Sorathia and A. R. Parikh;
Ind. J. Chem., **36B**, 822 (1997).

360. Ketan Hirpara, Satyan Patel, Ashutosh Joshi and Hansa Parekh;
Indian J. Heterocyclic Chem., **13(3),** 221 (2004).

361. A. V. Dobaria, J. R. Patel & H. H. Parekh;
Ind. J. Chem., **42B,** 2019 (2003).

362. B. P. Kansagara, H. H. Bhatt, A. R. Parikh;
Indian J. Heterocyclic Chem., **12,** 61-64, (2002).

363. H. S. Yathirajan, R. S. Narasegowda, P. Nagaraja and M. Bolte;
Acta. Cryst. (2005); E61, 0179-0181. (doi; 10. 1107-51600 536804033598).

364. Bente Frolund, Jeremy R. Greenwood, Mai M. Holm et. al;
Bioorg. & Med. Chem. vol.**13(18)** 5391-5398, (2005).

365. H. Bryan Norman, A. Peter Lander, M.Joseph Gruber et. al;
Bioorg. & Med. Chem. lett., vol.**15(24),** 5526-5530, (2005).

366. Jie-Fei Cheng, Mi Chen, Bin Liu, Zheng Hou, Thomas Arrhenius and Alex M. Nadzan;
Bioorg. & Med. Chem. Lett., **16(3)** 695-700, (2006).

367. J. A.Wiles, A. Hashimoto, J. A. Thanassi, J. Cheng, et. al;
J. Med. Chem., **49(1)**, 39-42 (2006).

368. Febung Anon;
Ber. **18,** 1814 (1885).

369. Wohler F. and Liebig;
J. Ann. **3,** 249, 267 (1832).

370. Poleuze;
J. Ann. **10,** 249 (1834).

371. G. Bram, A.Loupy, M.Pedouassaut;
Bull. Soc. Chim. Fr., **1**, 124-8 (1986); *Chem. Abstr.,* **105,** 190460g (1986).

372. Masanori Hatsuda and Masahiko Seki;
*Tetrahedron vol.***61(41)**, 9908-9917 (2005).

373. A. Stephen Dibiase,R. james Beadle and W.George Gokel;
Org. Syntheses, Coll. Vol. **7,** 108; Vol. **62,** P. 179 (2002).

374. A. K. Mohankrishna, M.C.Lakshmikantham, Dugal Carol;
Chem. Abstr., **128,** 282754j; (1999).

375. G. Bremanis Kolvins, I. Acena, I. E.Lukevics, M.Vereris, V. Kauss, P. Trapenstar, E. Lierins;
Chem. Abstr., **103**, 59761 (1985).

376. Tanaka Masato; Sakakura Toshi Yasu;
Chem. Abstr., **104**, 88317h (1986).

377. Satio Hiroshi, Hirose Kench;
Chem. Abstr., **108**, 55670 (1988).

378. Lai Hoi Kiong, Davis Robert Allan; Relyea Douglas Irving;
Chem. Abstr., **131(13)**, 170273q (1999).

379. Bormann Gerhard;
Chem. Abstr., **100**, 68184b (1984).

380. T. V.Stezhko, V. GGranik. R. G. Glushokov, L. F. Roshehina, A. I. Polezhaeva; M. O. Mashakovskii;
Kim Farm Zh. **18(3)**, 296-7 (1984) (Russ); *Chem. Abstr.,* **101**, 90704p (1984).

381. Uhlendorf Jochim, Leyck Sigurd, A. Nattermann;
Chem. Abstr., **100**, 68161s (1984).

382. M. Bimber Russell;
Chem. Abstr., **74,** 87655s (1971).

383. R. G. Shepherd;
U.S. 727149; *Chem. Abstr.,* **111,** 97104h (1998).

384. Kobayashi, Shigco, Tsuchida, Hiroyuki, Yinno Atusushi;
Jpn. Kokai Tokkyo koho JP **10,** 30035 (98 30, 035) (Cl. CO82 13/001) 3, Feb. (1998); (96/203, 0232 Jul. (1996) pp Japan); *Chem. Abstr.,* **128,** 155352b (1998).

385. M. C. Dougal Carol Lakshikanthan, Mohan Krishna A. K.;
Chem. Abstr., **128(23),** 28275j (1999).

386. Lai Hoi Kiong, Davis Robert Allan; Relyea Douglas Irving;
Chem. Abstr., **131,** 170273q (1999).

387. Yagihara, Tomio Kuchi, Tetsushi;
PCT Int. Appl. WO **02,** 64, 554 (Cl.CO7C. 327/44) (2002) ; *Chem. Abstr.,* **137,** 169325t (2002).

388. V. V. Norsyrava, B. A. Trotimov;
PCT Int. Appl. WO **49,** 148 (Cl. CO07D 87422) ; *Chem. Abstr.,* **136,** 216684a (2002).

389. Valmajer Juliya, Toplak Renata, Mujeen Le Marechal;
Fak. Za. Strojnisto Uni., **26,** 138 (2001); *Chem. Abstr.,* **134,** 207662y (2001).

390. Shibata Yasushi, Yagihara tomics Kashahars Ismmu;
Chem. Abstr., **134,** 602, 353299q (2001).

391. Parlo Sanna, Antonio Carta, Mohamma E. Rahbar;
Eur. J. Med. Chem., **35,** 535-43, (2000).

392. E. J.Iwanowicz, J. G. M.Dhar,; K.Leftheris,C.Liu;
U.S. US 6, 420, 430 (Cl. 514-374; CO7D 263/34), (2002); *Chem. Abster. ,* **137,** 9374ob (2002).

393. J. S.Ian Fairlamb, R.Laster Marrison, M.Julia Dickinson, Feng-Ju Lu and Jan Peter Schidt;
Bioorg. & Med. Chem., **12(15),** 4285-4299, Aug (2004).

394 Murakkami Hiroshi, Masuzawa Y., Takil S., Ito Toshinori;
Jpn. Kokai Tokkyo Koho JP (2003), 206, 281 (Cl. CO7D 231/12) (2003).

395. Atwal Karnails, J.Grover Gary, C.Ding Charles, P.Stein Philip, Woyd John, Ahmed Saleem, G. Hamann Lawrence, Green David, N.Ferrara Francis;
PCT Int. Appl. WO **03** 50, 261 (Cl. C12N); *Chem. Abstr.,* **139,** 53018g (2003).

396. Nurolaini Kifik, Erik De Clercqu, Jan Balzarini and Claire SImons;
Bioorg. & Med. Chem., **12(15)**, 4245-4252, Aug. (2004).

397. Marion Nipper, Yaorong Qian, R. Scott Garr and Karen Miller;
Chemosphere, **56(6)**, 519-530, Aug. (2004).

398. Miroslav Otmar, Milena Masojidkova, Ivan Votruba and Antonin tloy;
Bioorg. & Med. Chem., **12(12)**, 3187-3195 (2004).

399. S. Srinivasan, J. Annaraj. P. R. Athappan;
Journal of Inorganic Biochemistry, **99(3),** 876-882, March (2005).

400. Olivier Nicolas, Delphine Margeut, Nicolus Tauden, Michele Calas, Henri J. Vial and Francoise Bressolle;
Journal of Chromatography B, **820(1),** 83-89, June (2005).

401. Guohua Zhao, Prakash C. Taunk, David R. Magnin et. al;
Bioorg. & Med. Chem. lett., **15(18)**, 3992-3995, Sep. (2005).

402. Jon Bondebjerg, Henrik Fuglsang, Kirsten Rosendal Valeur, John Pedersen and Lars Naerum;
Bioorg. & Med. Chem. lett., **16(13)**, 3614-3617 (2006).

403. F. M. Bharmal, D. J. Kaneria and H. H. Parekh;
Indian J. Heterocycl. Chem., **12,** 279-80 (2003).

404. K. I.Mahan, T. A.Foderaro, T. L.Garza, R. M.Martinez, G. A.Maroney, M. T. Trivissono and E. M.Willuging;
Anal. Chem, **59**, 938 (1987).

405. J.Azuma, T.Katayama, T.Koshijima;
Wood Res., **1**, 76, (1989).

406. A.Gourdenne, A. H.Massarani, P.Manchaux, S.Aussudre and L.Thourel;
Polym. Prepr., **20**, 471 (1979).

407. S.Miyazaki, C.Yokouchi, M.Takada;
Chem. Pharm. Bull. Jpn., **37**, 208 (1989).

408. S. Paul, P. Nanda, P. Gupta;
Tetrahedrn Lett., **43(23)**, 4261-4265 (2002).

409. R. F.Alexandre, A.Bercibar, T. Besson;
Tetrahedrn Lett., **43(21)**, 3911-3913 (2002).

410. H. Koshima, K. Kutsunai;
Heterocycles, **57(7),** 1299-1302, (2002).

411. B.Stefance, M. Kocevar, S. Polanc;
Synth. Comm., **32(11)**, 1731-1734 (2002).

412. S. Caddick;

Terahdron, **51(38),** 10403- 10432 (1995).

413. V. M. Parikh;

"Absorption Spectrosocpy of organic molecules", addition-wesley pub. Co., London, 243-256 (1978).

414. C. N. R. Rao;

"Chemical application of infrared Spectroscopy" Academic press, New York (1963).

415. A. R. Kartizky and R. Alan Jones;

J. Chem. Soc., **2942** (1960).

416. F. V. Loffe;

Khim. Geterokeiki Sodein, **6**, 1089, (1968); *Chem. Abstr.*, **70,** 72338 (1986).

417. V. G. Thakare and K. N. Vadodkar;

Indian J. of Chem., **25(B),** 610-612 (1986).

418. A. L. Barry;

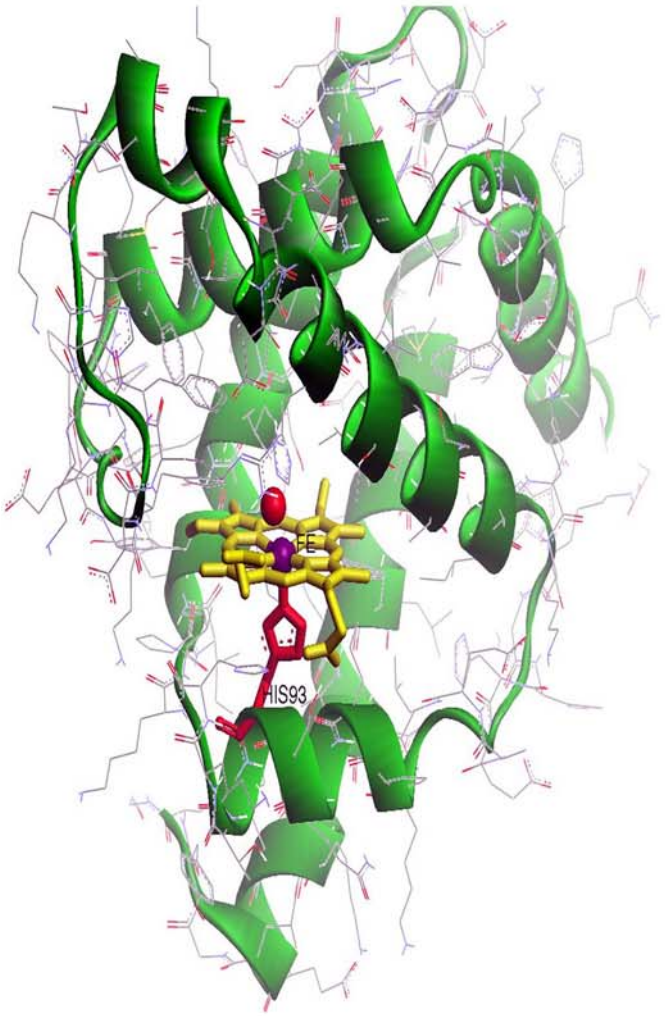
The Antimicrobial Suceptibility test Principle and Practices edited by Illus Lea and Febiger, *(Philadelphia Pel USA)* **180;** *Bio. Abstr.*, **64,** 25183 (1976).

419. N.D.Colphup,L.H.Daly and S.E.Wider;

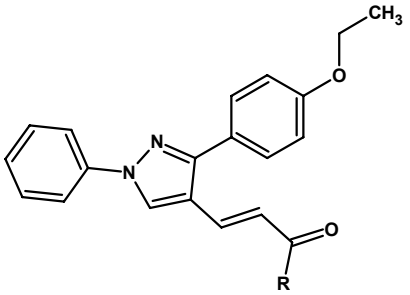
Itroduction to IR and Raman Spectroscopy,Academic Press Inter Edn.(1964).

420. Silverstein Bassler and Morrill;

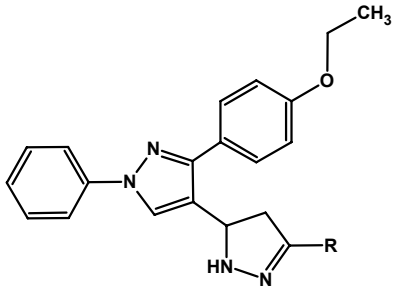
Spectrometric Identification of organic compounds fifth edition (1991) by John Wiley & Sons.



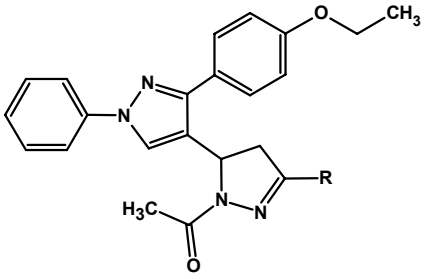
LIST OF NEW COMPOUNDS



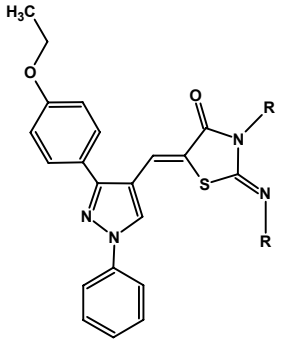
R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-



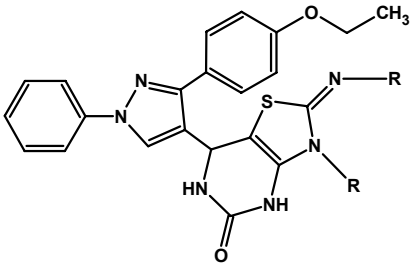
R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-

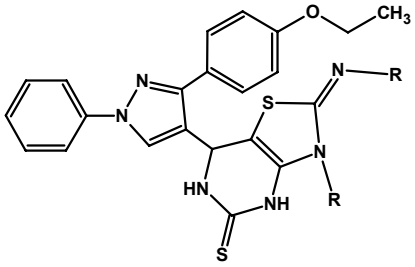


R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-

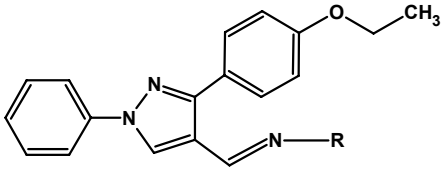


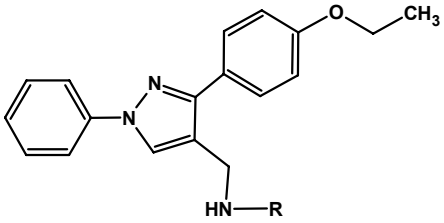
R
C_6H_5-
4-OCH_3-C_6H_4-
3-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-CH_3-C_6H_4-
4-OH-C_6H_4-
4-F-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
3,4-$(Cl)_2$-C_6H_4-
4-NO_2-C_6H_4-
3-NO_2-C_6H_4-



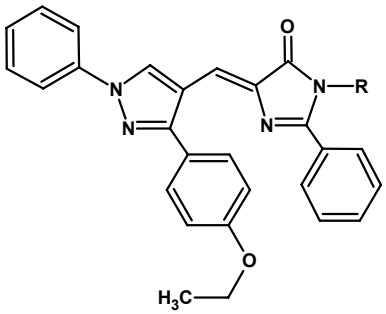


R	R
C_6H_5-	C_6H_5-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
3-OCH_3-C_6H_4-	3-OCH_3-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
3-CH_3-C_6H_4-	3-CH_3-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-
3,4-$(Cl)_2$-C_6H_4-	3,4-$(Cl)_2$-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-

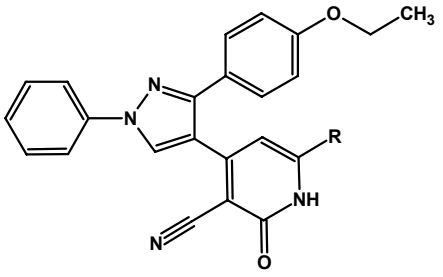




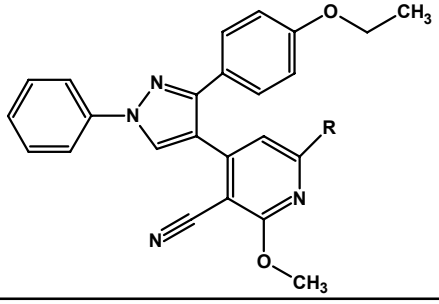
R	R
C_6H_5-	C_6H_5-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-
2-NO_2-C_6H_4-	2-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
2-CH_3-C_6H_4-	2-CH_3-C_6H_4-
2,4-$(Cl)_2$-C_6H_3-	2,4-$(Cl)_2$-C_6H_3-
3,4-$(Cl)_2$-C_6H_3-	3,4-$(Cl)_2$-C_6H_3-
2-OCH_3-C_6H_4-	2-OCH_3-C_6H_4-



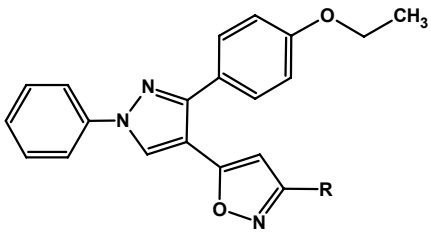
R
C_6H_5-
4-Cl-C_6H_4-
3,4-$(Cl)_2$-C_6H_3-
4-Br-C_6H_4-
4-F-C_6H_4-
3-Cl,4-F-C_6H_4-
2-OCH_3-C_6H_4-
4-OCH_3-C_6H_4-
2-CH_3-C_6H_4-
4-CH_3-C_6H_4-
2-NO_2-C_6H_4-
4-NO_2-C_6H_4-



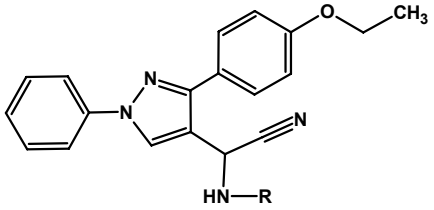
R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-



R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-



R
C_6H_5-
4-NH_2-C_6H_4-
4-Cl-C_6H_4-
4-Br-C_6H_4-
4-F-C_6H_4-
2-OH-C_6H_4-
4-OH-C_6H_4-
4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
2-C_4H_3S-



R
C_6H_5-
4-Cl-C_6H_4-
4-CH_3-C_6H_3-
4-Br-C_6H_4-
4-F-C_6H_4-
3-Cl,4-F-C_6H_4-
2-OCH_3-C_6H_4-
4-OCH_3-C_6H_4-
2-CH_3-C_6H_4-
3,4-$(Cl)_2$-C_6H_3-
2-NO_2-C_6H_4-
4-NO_2-C_6H_4-